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In the short space of four years synthetic detergents have made a tremendous change in the household washing habits of American housewives. At the start of 1948 they accounted for less than 10% of the "laundry soap" business; by the end of 1951 they accounted for over 60%. The product enjoying the greatest popularity in this classification (Tide) is currently being used by one woman out of every four who do their own dishes, and one out of every three who do their own laundry.

For your information the Chemical Division of The Procter & Gamble Company has prepared this article, discussing some of the differences between synthetics and soaps which formerly were widely used for household washing.

How synthetic detergents differ from soaps

Synthetic detergents are organic compounds with molecules whose opposite ends are highly polarized like those of soap; one end consists of the type of structure which is oil soluble, the other consists of the type which is water soluble.

Magnesium and calcium soaps formed by interaction of sodium soaps with water hardness are among the most insoluble of compounds. The precipitation which occurs with soap in hard water wastes soap and causes cloudy glassware and unsightly deposits. The "tailor-made" molecules of synthetics do not form these insoluble compounds in hard water. They, therefore, leave surfaces cleaner because they are free of any precipitated "soap film" formed during rinsing. Also, unlike soaps, in solution, synthetics can be used at almost any pH. Soaps, of course, must be kept at pH 10 or above, or they will split into fatty acids. Most synthetic products in general use have solution pHs from 6.0—10.0. Few are above the pH of soap.

The special washing abilities of synthetic detergents

As a consequence of the characteristics discussed above, synthetics are particularly well-suited for washing off acidic soils which would destroy soap. Since they aren't destroyed by hardness or by salts of other metals as soaps are, they are well-suited to washing a great variety of things which could be washed only with alkalis before—for instance, glass laboratory utensils.

The effect of synthetic detergents on bacteria

The synthetics in general and widespread use have about the same general effect on bacteria as soaps —that is, they have some germicidal effect on some strains, but for creating relatively sterile conditions, synthetic detergents rely more on removing bacteria than on killing them.

Detergents

The effect of synthetic detergents on skin

Over the past seven years Procter & Gamble has included these synthetic detergents in the continuing series of tests, designed to measure the effect of washing products on skin. In addition to the routine patch and arm-immersion tests, Procter & Gamble has conducted, under careful medical supervision, extensive clinical and home-usage tests of all its products, including the new synthetic detergents. These tests indicate that household detergents in use today, as a class, do not differ greatly in their effect on the skin from the general-purpose package soaps which have been used for years. Some have a lower pH than soaps and, hence, less effect on persons sensitive to alkali.

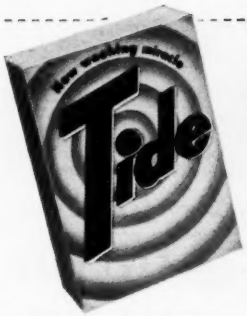
Like soaps, the detergents generally are mild primary irritants, but a fact not generally realized is that on the average person subjected to patch tests or immersion tests, most detergent solutions cause less skin reaction than do soap solutions.

Women have had many years in which to learn whether or not all soaps or certain soaps prove irritating in each particular case. Any problems arising from the effect of soap on skin have, therefore, been spread over decades. In the case of washday detergents, practically every woman in America was exposed to these products in a concentrated period of two or three years.

This great popularity and widespread use of synthetic detergents, together with their relative newness on the market, have resulted in a situation where synthetic detergents are likely to be suspected as the cause of many cases of dermatitis where they probably are not involved at all. With almost all housewives now using synthetic detergents for one or more purposes in their homes, it is inevitable that when a physician sees a case of hand dermatitis, a history of exposure to detergents will be obtainable. The significance of the dermatitis must be appraised against the background of the wide use of the detergent products.

For further information . . .

send for free booklet, "About Synthetic Detergents—Facts for Physicians." Write: The Procter & Gamble Co., Box 687B, Cincinnati 2, Ohio.



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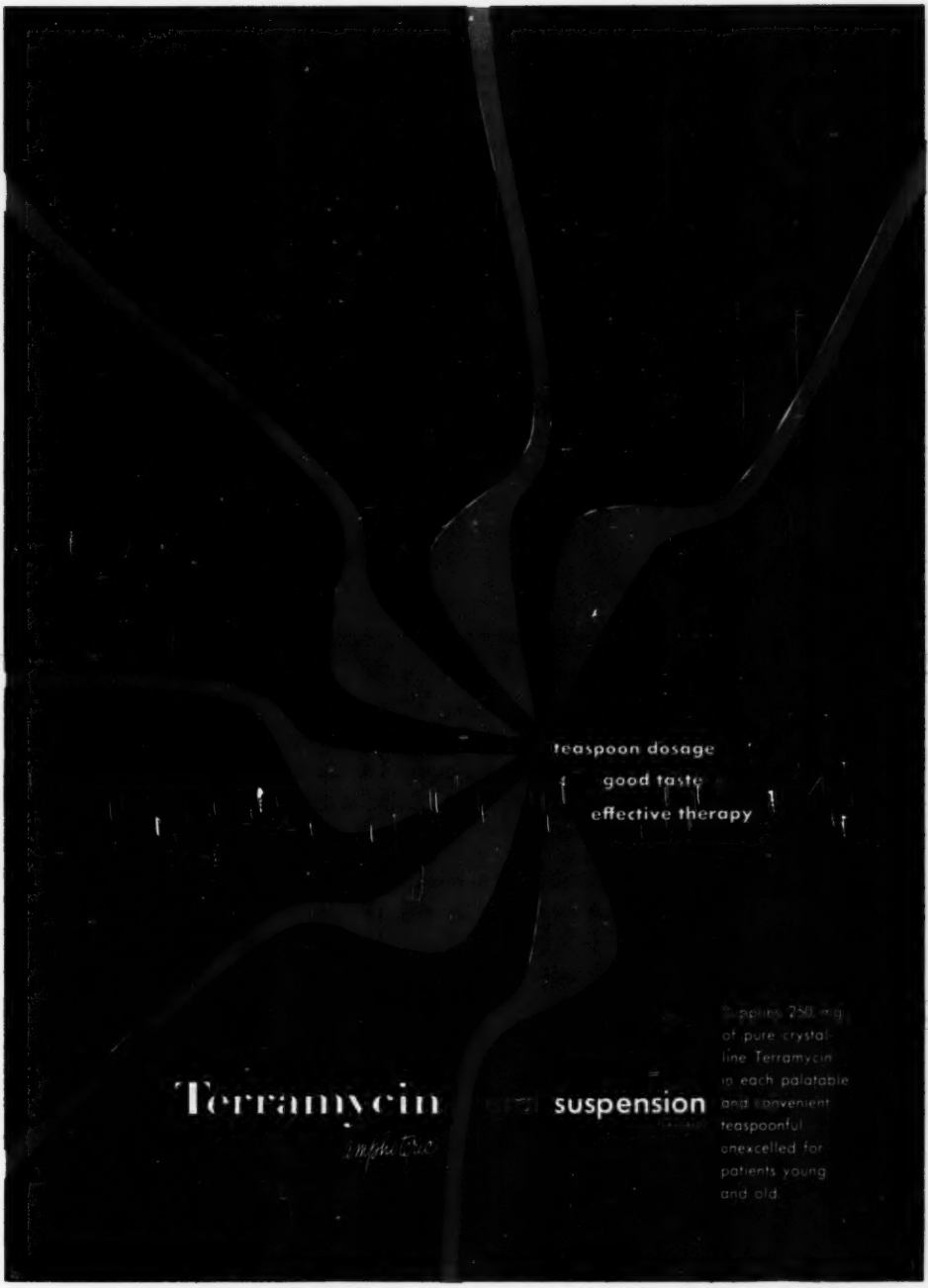
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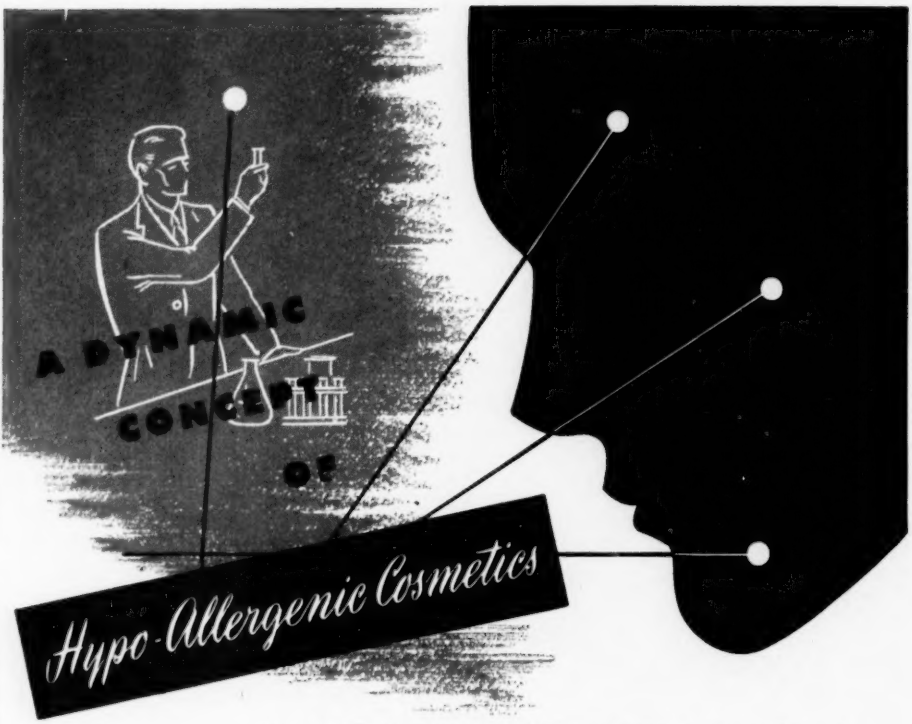

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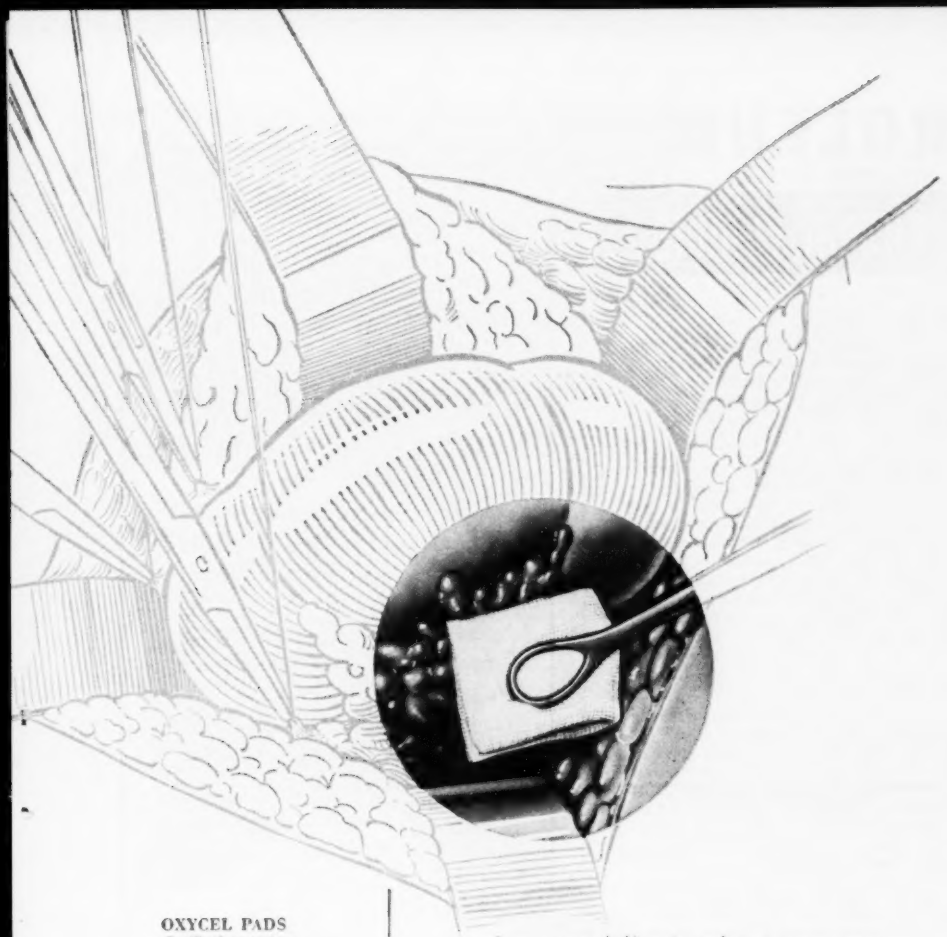

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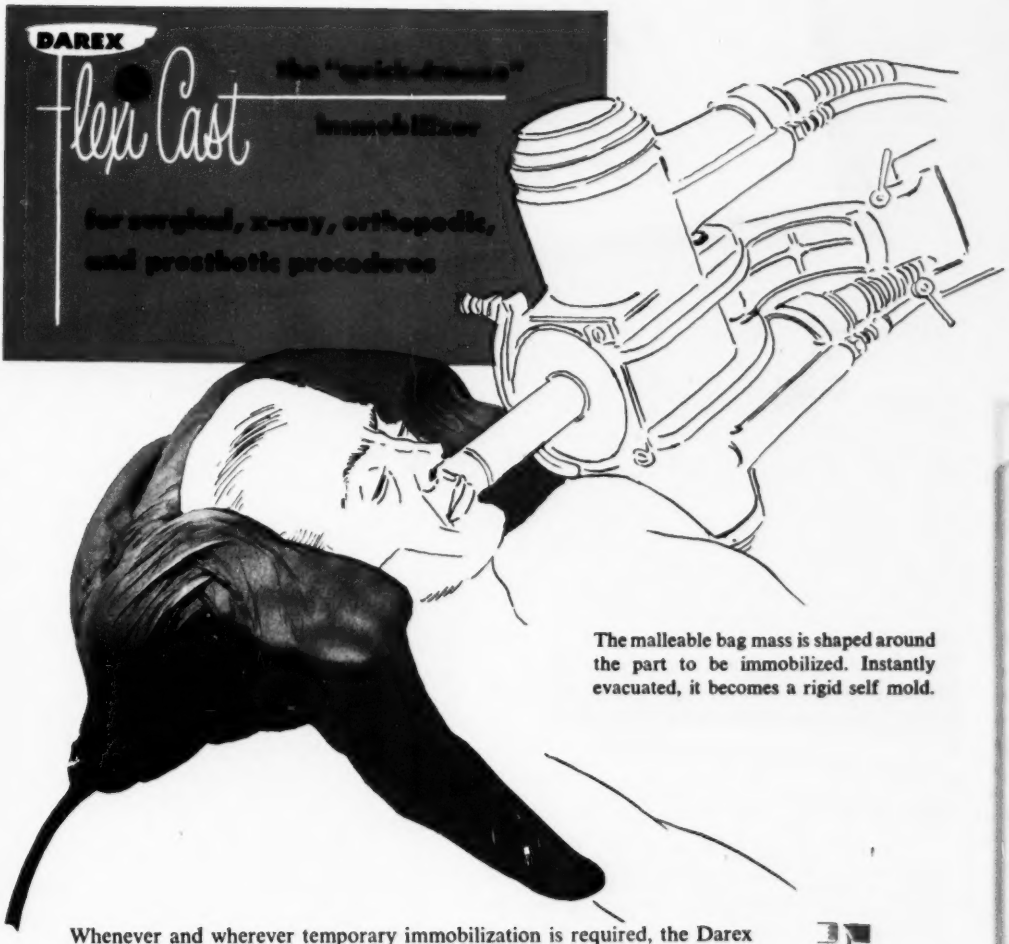

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1 Gross, Elmer R., M.D.; Wright, Carroll S., M.D.; Oral Bismuth Therapy in Syphilis and Various Dermatoses—Paper presented at the Pennsylvania Medical Society Meeting, October 8, 1946 at Philadelphia, Pennsylvania.

2 Gross, Elmer R., M.D.; Howles, James K., M.D.; Non-Specific Treatment of Dermatoses and Adjunctive Therapy of Syphilis with Oral Sodium Bismuth Triglycollamate. Read before the Section of Dermatology and Syphilology Meeting of the Centennial Meeting of the A.M.A. at Atlantic City, New Jersey, June 12, 1947.

3 Year Book of Dermatology and Syphilology, 1946, page 31.

4 Sawicky, H. H., M.D.; Bistrimate (sodium bismuth triglycollamate) Administered by Mouth in the Treatment of Chronic Discoid Lupus Erythematosus. The Journal of Investigative Dermatology, vol. 9 #3 September 1947.

5 Howles, James K., M.D.; Treatment of Inflammatory-Dermatoses with Oral Bismuth (sodium bismuth triglycollamate). Southern Medical Journal, vol. 41 #11, pages 1033-1041, November 1948.

6 Pascher, Frances, M.D.; Sawicky, H. H., M.D.; Silverberg, M.G., M.D.; and Emmet, Richard, M.D.; Bistrimate for Lupus Erythematosus, Lichen Planus and other Dermatoses. Journal of Investigative Dermatology, vol. 10, #6, June 1948.

7 Miller, Thomas H., M.D. and Delaney, James R., M.D.; Oral Bismuth therapy in Dermatology. Archives of Dermatology and Syphilology, Vol. 60, August 1949.

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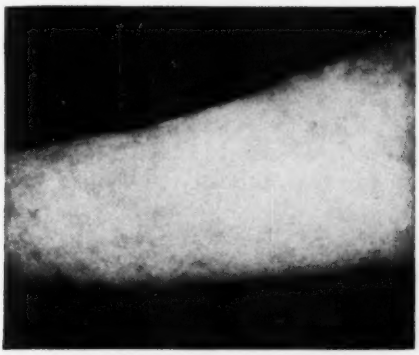

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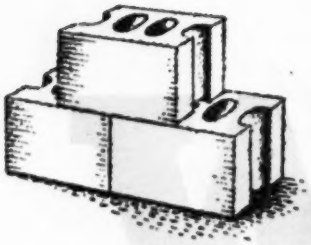

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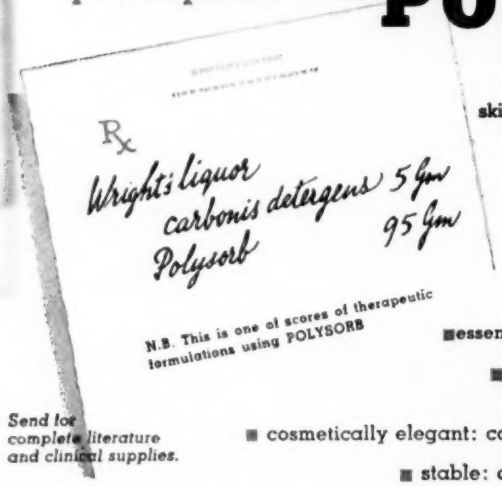
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MODES OF SPREAD OF CANCER OF SKIN

FREDERIC E. MOHS, M.D.
MADISON, WIS.
AND
THEODORE G. LATHROP, M.D.
OREGON CITY, ORE.

DURING the past sixteen years more than three thousand cancers have been removed by means of the microscopically controlled excisions which characterize the method which we have termed "chemosurgery."[1] A striking observation repeatedly made during the course of these excisions was that many external cancers exhibited irregular outgrowths which had not been detected by clinical visualization and palpation.

In some cases these "silent" extensions were due to a peculiar affinity of the cancer for some specific tissue structure which it would follow selectively for unexpectedly great distances. Some structures for which certain cancers showed particular affinity were the following: (1) dermis, (2) fascial planes, (3) periosteum, (4) perichondrium, (5) embryologic fusion planes, (6) nerve sheaths, (7) lymphatic vessels, and (8) blood vessels. In other cases no specific affinities were observed, but nevertheless irregular outgrowths were present, apparently as a result of the countless local variations in the mechanical and nutritive conditions for the spread of cancer.

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From the Chemosurgery Clinic, Department of Surgery, Wisconsin General Hospital and the McArdle Memorial Laboratory for Cancer Research, University of Wisconsin School of Medicine (Dr. Mohs).

1. (*a*) Mohs, F. E., and Guyer, M. F.: Pre-Excisional Fixation of Tissues in the Treatment of Cancer in Rats, Cancer Res. **1**:49, 1941. (*b*) Mohs, F. E.: Chemosurgery: A Microscopically Controlled Method of Cancer Excision, Arch. Surg. **42**:279, 1941; (*c*) Chemosurgical Treatment of Cancer of the Lip: A Microscopically Controlled Method of Excision, ibid. **48**:478, 1944; (*d*) Chemosurgical Treatment of Cancer of the Nose: A Microscopically Controlled Method, ibid. **53**:327, 1946; (*e*) Chemosurgical Treatment of Cancer of the Ear: A Microscopically Controlled Method of Excision, Surgery **21**:605, 1947; (*f*) Chemosurgical Treatment of Cancer of the Eyelid: A Microscopically Controlled Method of Excision, Arch. Ophth. **39**:43, 1948; (*g*) Chemosurgical Treatment of Cancer of the Face: A Microscopically Controlled Method of Excision, Arch. Dermat. & Syph. **56**:143, 1947; (*h*) Chemosurgical Treatment of Cancer of the Extremities and Trunk: A Microscopically Controlled Method of Excision, Arch. Surg. **57**:818, 1948; (*i*) Chemosurgical Treatment of Cancer of the Skin: A Microscopically Controlled Method of Excision, J. A. M. A. **138**:564, 1948; (*j*) Chemosurgical Treatment of Tumors of the Parotid Gland: A Microscopically Controlled Method of Excision, Ann. Surg. **129**:381, 1949; (*k*) Chemosurgery in Cutaneous Malignancy, California Med. **71**:173, 1949; (*l*) Chemosurgical Treatment of Melanoma: A Microscopically Controlled Method of Excision, Arch. Dermat. & Syph. **62**:269, 1950.

Regardless of whether the clinically unrecognizable outgrowths were due to specific affinities or whether they were due to more obscure factors, an appreciation of their frequent occurrence and an understanding of their nature are of obvious importance from the standpoint of therapy. In this article certain patterns of neoplastic spread will be described and illustrated by means of photographs, diagrams, photomicrographs, and reconstructions. These will indicate how cancers of a certain type located in a certain area will tend to act, but it is to be emphasized that each cancer has its own individual behavior pattern which cannot be appreciated fully except by systematic microscopic examination such as is afforded by the chemosurgical technic.

CANCERS WITH AFFINITY FOR THE DERMIS

Probably the commonest specific tissue affinity exhibited by cancer of the skin is for the dermis. The majority of the more highly invasive basal cell epitheliomas show some degree of predilection for this tissue; the predilection is considerably less commonly observed in less invasive basal cell epitheliomas and in squamous cell epitheliomas. Epitheliomas with a strong tendency to spread in the dermis are most commonly seen in the upper part of the face, namely, the forehead, temple, and scalp, but they are also common on the neck, nose, and other parts of the face.

Cancers showing strong affinity for the dermis may be found to radiate intradermal outgrowths for several millimeters or even centimeters from the main mass, while their spread into the deeper tissues may be minimal. Since the intradermal spread tends to take the form of a thin sheet of slender interspersing strands, the initial stages of this invasion are not clinically detectable by gross visualization and palpation. In time, however, the intradermal involvement of a given area becomes sufficiently thick to produce clinical signs, such as palpable induration, visible pearly tissue and ulceration, but by this time the clinically undetectable peripheral involvement has swept beyond.

The tendency to follow the dermis in a selective manner usually is most strikingly exhibited in more advanced lesions (Fig. 1), but it also may be observed in fairly early lesions. Since the clinically undetectable zone of spread tends to be wider around large lesions than around small ones, it follows that treatment, whether by surgical excision or by radiation therapy, should include a wider zone around large lesions than that around small lesions. With chemosurgical treatment, of course, excision is limited to the microscopically demonstrated limits of invasion and no extra tissue need be removed.

The width of the zone of "silent" intradermal invasion may vary at different points at the periphery of the cancer. In some cases extension may be several times as great on one side as on the other sides (Fig. 1), and in such instances the advantage of microscopically guided excision is particularly great.

CANCERS WITH AFFINITY FOR FASCIAL PLANES

Many cancers show a tendency to invade down to fascia and then spread peripherally in or on the surface of this tissue. For example, in one case the cancer arose on the dorsal side of the second metacarpophalangeal joint and extended to the palmar side of this joint. On clinical examination, it seemed almost certain that the cancer extended through the joint (Fig. 2*A*). However,

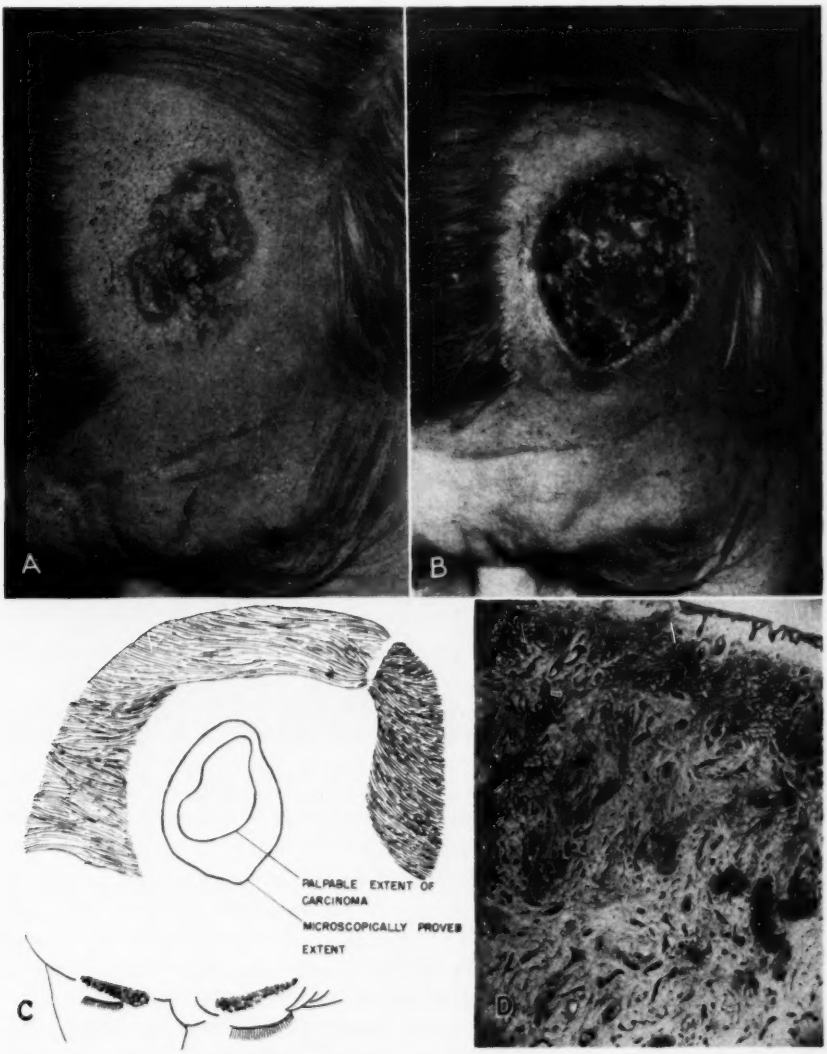

Fig. 1.—*A*, basal cell epithelioma, apparent size 31 by 51 mm. *B*, granulation tissue after chemosurgical excision showing that the cancer had spread peripherally for an unexpected distance (actual size 54 by 75 mm.) but that it had not invaded deeply. *C*, diagram showing the discrepancy between the palpable extent and the actual extent. *D*, photomicrograph of section from near the periphery showing the intradermal localization of the cancer.

upon chemosurgical removal it was found that the cancer had followed the surface of the fascia around the joint, which, accordingly, was not damaged (Fig. 2*B* and *C*).

Other examples may be cited. Cancer in the temporal region has been observed in many cases to invade to the temporalis fascia and then to spread peripherally, often with downward extension beneath the zygomatic arch, to the tendinous insertion on the mandible—all without invasion of the underlying temporalis muscle. In a case of basal cell epithelioma of the buttocks, the neoplasm extended upward in the fascial planes on the inner and outer sides of the external anal sphincter but spared the structure and the function of the muscle itself. In a case of squamous cell carcinoma in the parotid region a deep extension followed anteriorly along the fascia and perimesium of the stylohyoid muscle for an unexpected distance; such an extension would have been a sure source of recurrence

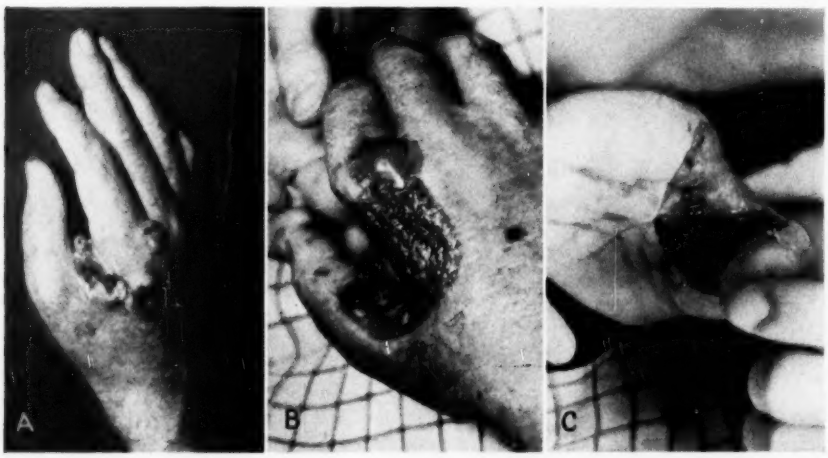

Fig. 2.—*A*, squamous cell epithelioma, recurrent after electrosurgical treatment. The mass extended around the metacarpophalangeal joint and appeared to extend into it. *B*, and *C*, granulation tissue after chemosurgical removal of the cancer which skirted around and completely spared the joint.

if it had not been followed out with the microscopic guidance provided by the chemosurgical technique. In several cases cancer overlying the sternocleidomastoid muscle has been observed to follow along the fascia around the anterior edge of the muscle. Apparently the resistance to the spread of cancer is less in this fascia than it is in the underlying muscle, which is rarely invaded.

An appreciation of the fact that cancer spreads along fascial planes and spares the underlying tissues, for a time at least, is often instrumental in the preservation of useful structures.

CANCERS WITH AFFINITY FOR PERIOSTEUM

Some cancers invade to the periosteum and then spread peripherally in this tissue. This phenomenon is most frequently observed in the "fixed" areas of the

face, where the skin closely overlies the underlying bone as on the temples, the malar eminence, the external auditory canal, the upper half of the nose, and in the inner canthal regions.

Numerous striking examples of the tendency of some cancers to follow periosteum have been observed. In the inner canthal region basal cell epitheliomas which have become rather advanced usually show a strong tendency to extend posteriorly along the periosteum of the medial wall of the orbit. Since the extension tends to be located largely in the region of the periosteum, it is usually unnecessary to damage the bulbus and the extraocular muscles during chemosurgical removal of the cancer.

In some cases the periosteal involvement is out of all proportion to the clinically detectable portion of the neoplasm. In a case of squamous cell epithelioma of the external auditory canal the neoplasm appeared to be localized to the lower half of the ear, but upon chemosurgical excision it was determined that there was a sheet of cancer in the periosteum of the temporal, parietal, and occipital bones, fully 10 cm. from the visible and palpable mass. In addition, the periosteum of the bony canal, the middle ear, and the canal of the Eustachian tube also was involved.

In another case, a basal cell epithelioma of the adenoid cystic type appeared to be largely localized to the temple, though there was some indefinite palpable thickening over the inferior rim of the orbit. Upon chemosurgical removal the cancer was found to have invaded the periosteum over much of the floor of the orbit, the roof of the antrum, and the nasal bone. In the orbit and antrum the thickness of the layer of cancer was greater than 1 cm., but in the more recently involved periosteum of the nasal bone the thickness was only 1 mm. In this, as in many other cases, the invasion of the periosteum was impossible to detect by palpation until the cancer had grown thick enough to cause gross irregularity in the outline of the bone.

CANCER WITH AFFINITY FOR PERICHONDRIUM

Epitheliomas overlying the cartilages of the nose or ear are sometimes observed to invade to the perichondrium and then spread out in this tissue. Owing to the thinness of the cutaneous and subcutaneous tissues of the ear, all but the very early cancers extend to the perichondrium, and not infrequently they invade more widely on the surface of the cartilage than they do in the more superficial tissues. The cartilage itself, like bone, provides a barrier to the deep spread of cancer, and it is only in the more advanced lesions that this tissue is penetrated. However, it is often necessary to remove cartilage because of the necessary removal of the overlying perichondrium.

Cancer of the nose as it invades the vicinity of the nasal cartilages may be deflected along the perichondrium, producing a neoplasm of very irregular shape. This irregularity, plus the circumstance of the similarity between the consistency of cancer and that of the tissues of the nose, accounts for the reputation of treacherousness associated with more advanced nasal neoplasms.

Affinity for perichondrium usually is not highly specific; rarely does the cancer extend in this tissue for more than 5 or 6 mm. beyond its advancing edge in the adjacent tissues. However, the strands of carcinoma invading this tissue often are very small in caliber and hence are not detectable by clinical examination.

CANCERS WITH AFFINITY FOR EMBRYOLOGIC FUSION PLANES

Epitheliomas arising over embryologic fusion planes may invade to an unexpected depth, owing, apparently, to the disposition of the condensed connective tissues in a direction perpendicular to the surface of the skin in these zones.

The most frequently observed lesion showing spread along a fusion plane is the common basal cell epithelioma of the nasolabial fold area. Neoplasms arising in this region and on the nasal ala often present a particularly troublesome therapeutic problem, first, because they tend to have a high degree of invasiveness and, second, because they are difficult to outline by palpation because of the similarity of the consistency of cancer and of the fibrocartilaginous tissues of the nose. A third factor which adds to the difficulty is the strong tendency for the deeper lesions to invade the embryologic fusion plane. The direction of invasion is in a plane which lies perpendicular to the skin of the cheek (Fig. 3).

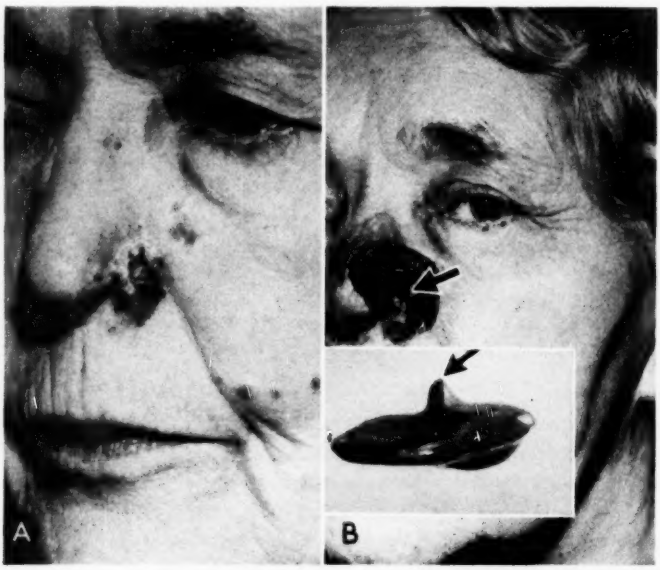

Fig. 3.—*A*, basal cell epithelioma, recurrent after x-ray and radium treatment. *B*, granulation tissue after chemosurgical excision, showing the depth of extension into the embryologic fusion plane (arrow). Insert shows a reconstruction of the cancer. The photograph, which was taken from above, shows the shape of the extension into the embryologic fusion plane (arrow).

Another place in which certain cancers invade particularly deeply is the fusion plane marked by the fold between the upper lip and the cheek. Also, cancer in the midline of the skin of the lower lip and chin often exhibits inordinately deep invasion, probably because of the better conditions for neoplastic spread in the sagittal plane of fusion.

CANCERS WITH AFFINITY FOR NERVE SHEATHS

Some epitheliomas exhibit a striking tendency to send out extensions in the nerve sheaths. In some cases one or more nerves may be selectively followed for several centimeters (Fig. 4). Usually, the cancer is in the form of a cylinder, several

cells thick, surrounding the nerve just beneath the perineurium (Fig. 4*E*); near the point of exit from the main mass of cancer, there also may be involvement of the epineurium and endoneurium (Fig. 4*D*).

The selective affinity for nerve sheaths seems to be an inherent characteristic of the individual cancer. Thus, two neoplasms of the same histologic type and with equal access to the same nerves may behave dissimilarly, with the one having a strong tendency to follow the nerves and the other having absolutely no such tendency.

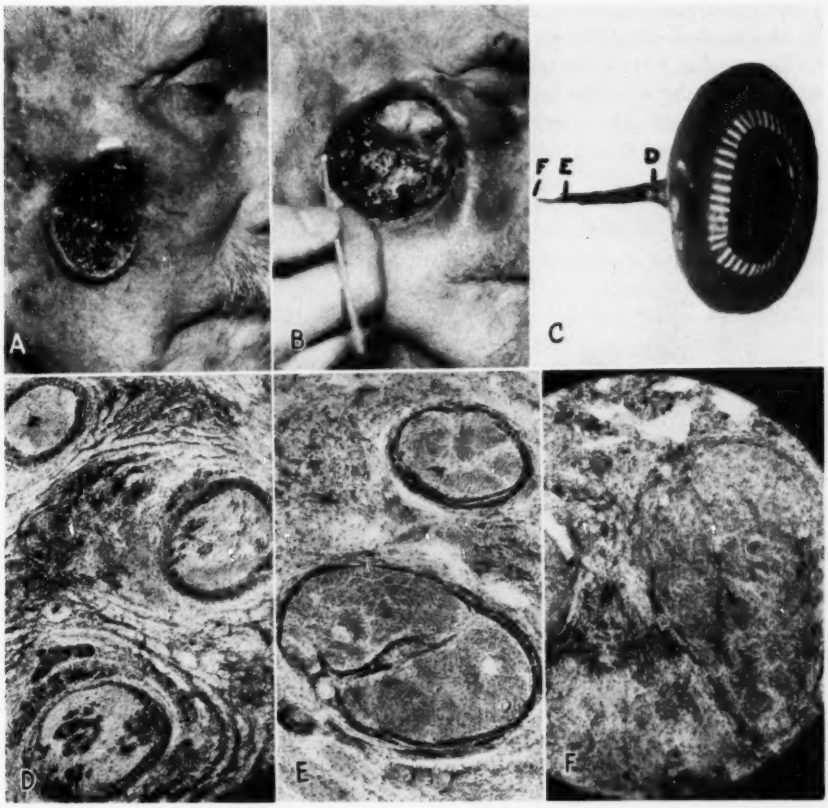

Fig. 4.—*A*, squamous cell epithelioma, recurrent after radium treatment. There was some weakness of the lower eyelid. *B*, granulation tissue after chemosurgical excision. An applicator is inserted in a sinus which was tunneled out while following an involved nerve into the parotid gland. *C*, reconstruction of the cancer showing an outgrowth which extended for 5 cm. along a branch of the facial nerve. *D*, photomicrograph of a section taken near the main mass showing cancer invading the epineurium as well as the perineurium. *E*, photomicrograph of the same nerves but near the termination of the cancer in the parotid region showing the exclusive localization in the perineurium. *F*, photomicrograph of the same nerves in the middle of the parotid gland just beyond the farthest extension of the cancer.

This affinity of some epitheliomas for nerve sheaths is such a striking phenomenon that it is surprising that no mention of it can be found in the literature. Of course,

the spread of carcinoma of the prostate in the perineural lymphatics is well known,[2] and there have been references to the perineural spread of cancer of the lip[3] and of the salivary glands.[4] Probably the chief reason why the perineural spread of cancer of the skin has not been observed previously is that prior to the development of chemosurgery there was no convenient way to make a systematic study of the microscopic features of the periphery of these neoplasms.

Despite the fact that the extension of epithelioma along nerve sheaths is a hitherto unreported phenomenon, it is not rare. In our series the incidence of selective affinity for the perineurium was 2.5% for squamous cell epithelioma (20 of 807 cases) and 1% for basal cell epithelioma (17 of 1,686 cases). Incidentally, the incidence of nerve sheath spread in our series of squamous cell epithelioma of the lip was 2% (10 of 508 cases), while in our series of cases of carcinoma of the parotid gland the incidence was 18.5% (5 of 27 cases). The phenomenon also was observed in two cases of sarcoma.

It should be pointed out that these series included an unusual proportion of cases of advanced lesions, and in fully a third of the cases there had been recurrence after previous surgical or radiation treatment elsewhere. Of the patients with squamous cell epitheliomas which showed selective affinity for nerve sheaths, 62% had received previous surgical or radiation treatment, while of those with basal cell epithelioma 16 of the 17 had received previous surgical and/or radiation therapy. Whether previous treatment enhanced the likelihood for perineural invasion or whether perineural spread was inherently associated with the more troublesome, recurrent lesions has not been demonstrated, but the latter seems most likely. The squamous cell epitheliomas with affinity for nerve sheaths had a higher than average malignancy as indicated by the following figures: grade 1, no cases; grade 2, 28.5%; grade 3, 66.7% grade 4, 4.8%. All the basal cell epitheliomas with spread along nerves were classified as "highly invasive." Many of these lesions showed signs of increasing malignancy, anaplasia, and metaplasia such as are often observed following repeated unsuccessful treatment with x-rays or radium.

From the information now available, it is uncertain whether the tendency of certain cancers to follow nerves is due to mechanical factors or whether it is due to nutritional factors; possibly both are involved. That the cleavage plane between a nerve and its sheaths provides a path of decreased mechanical resistance is indicated by injection experiments in which dyes and radiopaque materials were observed to follow a cleavage plane between the perineurium and the nerve fibers for considerable distances.[5] On the other hand, it is well established that nerves require adequate nutrition along their entire lengths and that this is assured by an efficient vascular network with both longitudinal and regional sources of supply.[6]

2. Warren, S.; Harris, P. N., and Graves, R. C.: Osseous Metastasis of Carcinoma of the Prostate with Special Reference to the Perineural Lymphatics, Arch. Path. **22**:139, 1936.

3. Figi, F. A.: Epithelioma of the Lower Lip: Results of Treatment, Surg., Gynec. & Obst. **59**:810, 1934.

4. Dockerty, M. B., and Mayo, C. W.: Primary Tumors of the Submaxillary Salivary Gland with Special Reference to Mixed Tumors, Surg., Gynec. & Obst. **74**:1033, 1942.

5. Sullivan, W. E., and Mortenson, O. A.: Visualization of the Movement of a Brominized Oil Along Peripheral Nerves, Anat. Rec. **59**:493, 1934. Saito, M.: Normal Shadow of the Peripheral Nerves and Their Pathological Change in Injury and Tumor, Am. J. Surg. **26**:300, 1934.

6. Adams, W. E.: The Blood Supply of Nerves, J. Anat. **76**:323, 1942.

The fact that some cancers have the tendency to follow nerves while others do not suggests the possibility that some obscure nutritional factor may be in operation. Possibly of similar significance is the fact that cancer in nerve sheaths often has a different histologic appearance from that in the other tissues; this is particularly evident in squamous cell epithelioma, which invariably loses part or all of its differentiation, with the result that only rarely is keratinization observed. Basal and squamous cell epitheliomas often have a similar histologic appearance when in the nerve sheaths, even though their appearance is quite different when growing in other tissues. These peculiar features indicate that undoubtedly there is much that is not understood about the mechanism of this mode of cancerous spread.

Obviously, the tendency to follow nerves would tend to have an adverse effect on the prognosis except when excision is microscopically guided as by the chemosurgical method, and even then some lesions prove hopeless as in two cases in which the perineural extension followed the facial nerve into the stylomastoid foramen. Cases of carcinoma of the lower lip with perineural extension into the mental foramen and thence along the inferior dental canal may also present formidable, though often not insurmountable, difficulties.

CANCERS WITH AFFINITY FOR LYMPHATIC VESSELS

Although the spread of cancer of the breast by permeation through lymph channels has been recognized for many years,[7] this mode of spread is apparently not widely recognized as far as cancer of the skin is concerned. Of course, the peripheral embolic spread of melanoma in the lymphatic vessels of the skin as manifested by satellite nodules, is well known. (In our series of 28 cases of melanoma this type of spread was demonstrably present in one case.) That squamous cell carcinoma also may exhibit peripheral embolic spread is not generally realized, but in our series of 807 cases of squamous cell epithelioma it was observed in five cases. The rarity of this discontinuous, embolic type of spread is fortunate because it has a definitely adverse effect on prognosis even with the microscopically controlled excisions afforded by the chemosurgical technique. When embolic spread in the lymphatics occurs, treatment should include the removal of a wide peripheral zone, and, when possible, a dissection of the regional lymph nodes.

Spread of epithelioma by permeation through lymphatic vessels may take place in two different ways. Either it may spread as a sheet of cancer by permeation of the small vessels of a lymphatic plexus, or it may follow one or more larger lymphatic vessels. The tendency to follow lymphatic plexuses is not infrequently observed in and around the nose and in the scalp (Fig. 5), while the tendency to follow larger trunks is most commonly observed in the preauricular and upper cervical regions.

Permeation by continuity through the lymphatic vessels may be observed in either basal or squamous cell epitheliomas. In the latter, the presence of cancer in the lumens of lymphatic vessels is of rather serious prognostic significance because of the danger of metastasis. However, no instance of metastasis has been observed in our series of cases of basal cell epithelioma with lymphatic permeation.

7. Handley, W. S.: Cancer of the Breast and Its Treatment, New York, Paul B. Hoeber, Inc., 1922.

CANCERS WITH AFFINITY FOR BLOOD VESSELS

The affinity of cancer for blood vessels may be manifested in two ways: (1) by invasion along the adventitia of arteries and veins and (2) by permeation through the lumens of blood vessels.

Selective affinity of cancer for the adventitia has been observed in seven cases of squamous cell epithelioma and in two cases of basal cell epithelioma. Usually the degree of selectivity is slight, but in several cases the adventitial extensions continued for 1 or 2 cm. beyond the main mass of cancer (Fig. 6*A*).

Epitheliomas with a tendency to spread in the lumens of blood vessels are extremely rare. Our series includes two cases, one of squamous cell (with cerebral metastasis) and one of basal cell epithelioma. In the latter case, many arteries and

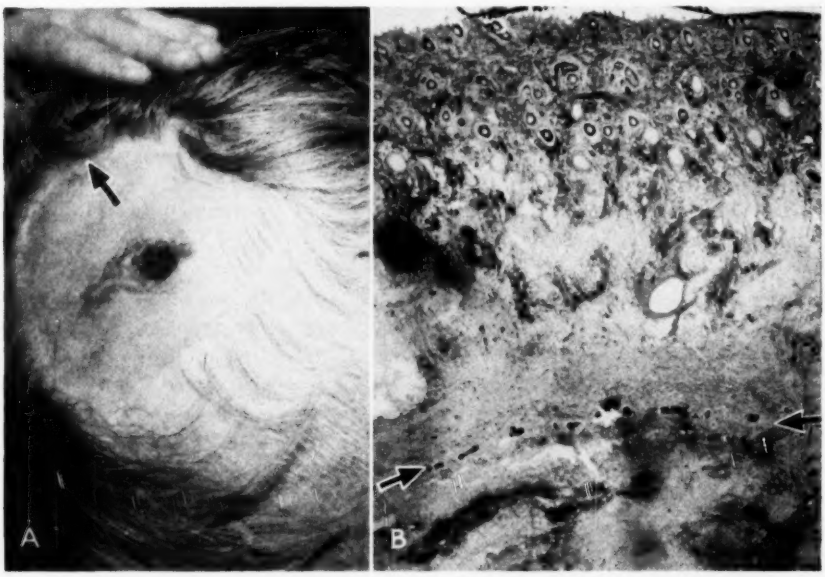

Fig. 5.—*A*, basal cell epithelioma that had recurred in the center and at the edge of a graft. The peripheral recurrence (arrow) was not clinically detectable. *B*, photomicrograph showing invasion in a lymphatic plexus just above the galea at the edge of the graft.

veins in the region of the nasolabial fold were permeated and in the deeper portions of the neoplasm the downgrowths were exclusively intravascular (Fig. 6*B*). There has been no evidence of metastasis in this case after four years.

CANCERS WITH IRREGULAR SPREAD BUT WITH NO SPECIFIC TISSUE AFFINITIES

It is common to observe the very irregular permeation of an epithelioma into the surrounding tissues, even though no specific affinity for any particular tissue structure can be demonstrated. Apparently there is considerable local variation in the mechanical and nutritional conditions which favor permeation by neoplastic tissue.

As would be expected, dense tissues, such as bone, cartilage, tendons, and aponeuroses, offer a barrier to the spread of neoplasms. For example, a sarcoma of the scalp spread widely over the top of the cranium before it penetrated the bone and then it followed two paths of lesser resistance: one, through a trephine hole (the site of a previous biopsy), and the other, through the coronal suture line.

As was mentioned in the section on spread along fascial planes, muscle also may constitute a barrier to the spread of cancer. This apparently is not due to any particular antagonism of muscle tissue for cancer tissue, because in some cases cancer has been observed to enter a muscle bundle and spread for some distance along its length. The effect more probably is mechanical. This conclusion is borne out by the frequent observation that cancer spreads more readily along the long direction of a muscle than it does in a direction perpendicular to the muscle fibers.

Not infrequently cancer is observed to extend more readily in the direction of softer tissues. This is commonly seen in lesions on the root of the nose and in

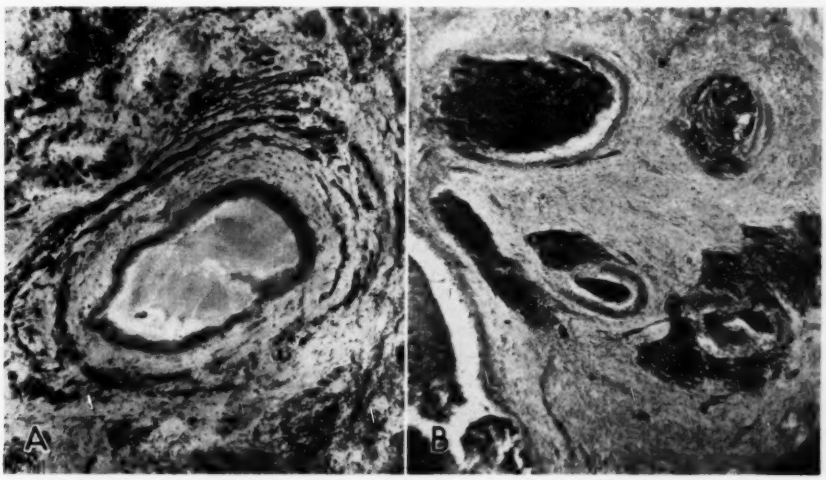

Fig. 6.—*A*, squamous cell epithelioma in the adventitia of a blood vessel. The cancer was in the region of the nasolabial fold. *B*, basal cell epithelioma located exclusively in the lumens of blood vessels. The cancer was in the region of the nasofacial fold.

the inner canthal regions; these neoplasms often extend farther in the direction of the soft tissues of eyelids than it does in the direction of the firmer tissues of the nose.

External factors may also influence the direction of the spread of cancer. For example, in a case of basal cell epithelioma just lateral to the depression made by the nosepiece of the patient's glasses, the neoplasm was found to have followed around the lower edge of the depression. Apparently, the pressure of the glasses had hindered the spread of the cancer through the depressed area.

The spread of cancer through tissues which have been irradiated heavily with x-rays or radium is often less rapid than in adjacent nonirradiated tissues. Here there probably is a combination of the mechanical barrier produced by the scar tissue and the nutritional deficiency occasioned by the closure of vessels due to endarteritis.

Subcutaneous fat, with its relatively poor vascular supply, is not a particularly favorable host for neoplastic invasion; therefore, downgrowths often may be observed to follow the fibrous septa which join the skin to the deep fascia. It is difficult to determine whether this preference is due to the presence of mechanical cleavage planes in the fibrous tissues or whether it is due to the better nutritive conditions occasioned by the blood and lymph vessels which are included in these septa. Probably, both mechanical and nutritive factors are operative.

COMMENT

From the standpoint of therapy the chief significance of the fact that many epitheliomas send out "silent" extensions is that these outgrowths if not recognized may be the cause of recurrence following surgical or radiation treatment. However, since these invading strands of tissue are in continuity with the main mass of cancer, their sure removal may be accomplished by means of the chemosurgical technique, with its complete microscopic control of excision.

Unrecognized outgrowths are frequently associated with epitheliomas having a high degree of invasiveness, and they are relatively uncommon in those with a low degree of invasiveness. As would be expected, the slender strands or thin sheets which characterize the advancing edge of a highly invasive cancer would be much less visible to the naked eye than the lobular outgrowing masses which characterize the less invasive neoplasm which grows more by expansion than by infiltration.

By what mechanism does a cancer select one pathway of spread in preference to another? Naturally, there is the circumstance of position which allows the tumor to have access to the tissue structure in question. Probably this factor accounts for the high incidence of cancers which show affinity for the dermis, because this is the first tissue encountered by the invading epithelioma. Necessarily, before a cancer can follow a fascial plane, periosteum, perichondrium, or other deeply situated tissue it must invade to the level of these structures. Ordinarily, cancers do not follow nerve sheaths until the larger nerve trunks are encountered; perhaps, this in part explains the great frequency of perineural spread associated with carcinoma of the parotid gland, which lies in close proximity to the facial nerve, and with carcinoma of the prostate, which has a rich nerve plexus.

However, there are other deciding factors besides position, because many cancers which have had access to these various structures have exhibited no particular affinity for them. Whether or not a given cancer is destined to spread in some specific tissue seems to be an inherent characteristic of the individual neoplasm, and it is impossible to predict definitely what will be the pattern of spread in the individual instance. The only allowable generalization is that strong specific histotropism is much more likely to be observed in association with the more highly invasive epitheliomas, whether of basal or of squamous cell type.

It seems probable that both mechanical and nutritional factors are operative in determining the direction of neoplastic spread. That there are numerous cleavage planes in which injected fluids tend to spread out more readily than in the adjacent tissues is easily demonstrable, and it is not surprising that the same planes should offer diminished resistance to the spread of some cancers. However, it is usually along these planes that the blood and lymph vessels travel, and it may be argued

that these supply more favorable nutritive conditions for neoplastic growth. Probably a combination of mechanical and nutritional factors always is operative, but one or the other may predominate, as determined by the location and by the characteristics of the individual neoplasm.

It may be speculated that cancer tissue produces spreading factors, such as hyaluronidase, which may have variants that decide which tissue a given neoplasm may selectively follow, but there are no published observations concerning this particular problem. That some neoplasms do contain spreading factors was demonstrated first by Duran-Reynals and Stewart [8] and more recently by McCutcheon and Coman,[9] but a constant relationship between the content of hyaluronidase and the degree of invasiveness of neoplasms has not been established.[10] In fact, there is recent evidence that most of the hyaluronidase activity found in cancers may be produced by contaminating bacteria.[11]

SUMMARY AND CONCLUSIONS

In the course of the chemosurgical excision of over 3,000 epitheliomas, it has been observed that a considerable proportion of these neoplasms exhibit irregular, clinically undetectable outgrowths into the surrounding tissues.

In some cases these "silent" outgrowths follow specific structures, of which the most noteworthy are the following: (1) dermis, (2) fascial planes, (3) periosteum, (4) perichondrium, (5) embryologic fusion planes, (6) nerve sheaths, (7) lymphatic vessels, and (8) blood vessels. In other cases irregular outgrowths may occur as a result of the numerous local variations in the mechanical and nutritional conditions which favor the spread of neoplasms.

Regardless of the mechanism by which these unpredictable extensions develop, it is important that their frequent occurrence be appreciated by everyone who treats patients with epitheliomas. Certain patterns of spread which often are observed in certain regions have been described, but it must be emphasized that each individual cancer has its own peculiar behavior pattern, which is not definitely predictable. It is because of this unpredictability of the pattern of spread of epithelioma that chemosurgery, with its complete microscopic control of excision, offers the best chance of cure and, at the same time, maximal conservatism.

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GERMAN SCHOOLS OF DERMATOLOGY IN THE PAST CENTURY

HANS M. BULEY, M.D.
CHAMPAIGN, ILL.

IN SURVEYING the historical development of a certain period of human achievement, one tries to understand how events came to pass, what their causes were, and what the forces were that caused them to take place in a particular manner. In doing so, great difficulties are soon encountered because of the multitude and complexity of the circumstances at work. At first, one focuses all attention on the outstanding personalities, the heroes of history, as the great movers and agitators, only to find after a more careful survey that they, on their part, were also subjected to the forces brought to play upon them by the thoughts and acts of their contemporaries. This Tolstoian idea occurred to me soon after I had become preoccupied with the history of German dermatology, and it became the leading motif of this review.

At the beginning of the 19th century, we find the German intellect, by and large, notably ill-prepared for scientific research. Since the Reformation, the philosophical faculties of the German universities had achieved a predominant position, and they exercised a marked influence on the general direction of studies, on method as well as content. These philosophical faculties, dominated by the idealism of Kant, Fichte, and Schelling, encompassed the fields of classical philology, history, mathematics, and, to a certain extent, the natural sciences. Their curricula were universal and all-inclusive, and it was in these fields that the student sought to achieve the ultimate in intellectual expression. The medical faculties, though they often taught chemistry, botany, and natural history, could not escape from this philosophical dominance. The stronger the philosophical faculties grew, the more directive and influential they were even upon the specialized fields. Unfortunately, the flowering of mysticism and romanticism in philosophy as well as in literature, at the turn of the century, was a deterrent to the development of a scientific attitude.

Among the physicians, the traditional concepts of Galen's humoral pathology and of Arabian teachings were still popular, and these were molded to fit the mood of the era. Physicians interested in skin diseases limited their work to translations of French and English authors. Their systems of classification were modified, and their terminology was changed. The natural-philosophical school of medicine, for example, considered exanthems "incomplete organisms or partly successful attempts to form eggs" (J. F. Meckel, 1815). The natural-historical school of K. W. Stark

From the Department of Dermatology of the Christie Clinic.

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and Schoenlein, including the latter's pupil, Konrad Heinrich Fuchs, tried to apply botanical concepts to the field of dermatology by creating a "flora nosologica" in imitation of Linnaeus' botanical system. There were families and species of diseases; there were blossoms and fruits of internal diseases.

A gradual change, however, began to take place. Objectively descriptive reports appeared, at first sporadically, later in greater numbers, in medical literature. For many years a marked dualism, a peculiar combination of romanticism and rationalism, resulted. The remnants of this strange mixture in German intellectual life can be traced to modern times and often render the understanding of the German mentality difficult for the non-German.

Alexander von Humboldt, the famous naturalist and world traveler, presented an excellent illustration of the metamorphosis in the German scientific thinking of that period. In 1795 he was deeply preoccupied with a problem which at that time stirred all intellectuals, the theorem of the so-called vital power. But two years later he stated in one of his letters: "One begins to convince oneself that some time experiments might become the basis for the practice of medicine. . . ." And, in another letter, he wrote: "Facts will remain constant, when the building of theoretical teaching, hurriedly constructed, has collapsed long ago."

During the following years, the voice of exact science became increasingly audible. Among the medical men, the physiologists and anatomists took the leading position in Germany. Johannes Mueller (1801-1858), professor at Bonn and later at Berlin, initiated the study of physiology as a logical introduction to the study of medicine and outlined the fundamental methods of medical research. Justus von Liebig (1803-1873), in Giessen, introduced and emphasized laboratory teaching in medicine. With reference to the skin, the physiologist at Breslau, Johannes Evangelista Ritter von Purkinje (1787-1869), studied the papillary lines of the palm (1823) and later (1833) the sweat ducts. Ernst Friedrich Gurlt (1794-1882) gave the first complete description of the sweat apparatus (1835). The anatomist Ernst Heinrich Weber reported on the tactile apparatus and its functions in 1834. Carl Herrmann Hertwig (1798-1881), in 1835, published comparative anatomical studies of the skin of man and animals.

In Vienna, the great pathologist Karl Rokitansky (1804-1878) made medical history with his pathologic studies based on a large number of autopsies, personally performed and recorded, although his system of general pathologic processes was still tinted with traditional unrealistic concepts. His colleague and friend, the internist Josef Skoda (1805-1881), applied Rokitansky's work to the field of internal medicine with great success. Johann Lucas Schoenlein (1793-1864), the internist at Würzburg and later in Berlin, though the protagonist of the natural-historical school, discovered a fungus to be the cause of favus and thus started the long series of mycological discoveries. Finally, at mid-century, the German pathologist, Rudolf Virchow (1821-1902), emancipated himself from all traditional teaching. He followed Rokitansky's methods of factual investigation but completed his work by creating a system of cellular pathology which became the foundation of modern medical science.

In view of the fundamental changes in scientific methods and ideas, one cannot be surprised to find dermatology moving in the same direction. The new trend inspired

all men with dermatological interests, rather than just a few leaders. Julius Rosenbaum (1807-1874), while a young lecturer at Halle in 1837, expressed his amazement that, in spite of the most detailed clinical descriptions of skin diseases, nobody had ever investigated the anatomical changes in the skin responsible for the abnormal conditions. Hermann Lebert, professor at Zurich, in 1845 and in 1848, had presented "a purely pathologic-anatomical classification of skin diseases in which inflammations, other nutritional disturbances, new formations, and parasites were employed in accordance with the most recent and finer research methods."

It is no wonder, then, that we find dermatological activities gaining remarkable momentum where research and teaching centers offered hospital facilities to promote systematic study. But, unfortunately, the number of such institutions was

	1st GENERATION	2nd GENERATION	3rd GENERATION	4th GENERATION
CLINIC HEADS	Ferd. v. Hebra 1816-1880	M. Kaposi 1837-1902	G. Riehl 1855-1943	L. Arzt
ASSOCIATES		H. A. Auspitz 1835-1886 Hans v. Hebra 1847-1902 F. J. Pick 1834-1910 (Prague) E. L. Schwimer 1837-1898 (Innsbruck & Graz) Isid. v. Neumann 1832-1906	Ed. Spiegler 1860-1908 Fr. Luithlen 1869-1927 V. Lukasiewicz 1860-1924 (Innsbruck & Lemberg) K. Kreibich 1869-1932 (Graz & Prague) E. Finger 1856-1939	W. Pick L. v. Zumbusch O. Kren L. Kumer G. Riehl Jr. H. Fuhs W. Kerl and others
CLINIC HEADS	K. L. v. Sigmund 1810-1883	Isid. v. Neumann 1832-1906	E. Finger 1856-1939	W. Kerl
ASSOCIATES		F. Mračeck 1848-1908	R. Matzenauer 1869-1932 (Graz) J. H. Rille (Innsbruck & Leipzig) S. Ehrmann 1854-1926	M. Oppenheim V. Mucha B. Lipschuetz J. Kyrle R. O. Stein G. Scherber H. Hecht and others
CLINIC HEADS	Herm. v. Zeissl 1817-1884	Ed. Lang 1841-1916 (from Innsbruck)	S. Ehrmann 1854-1926	G. Nobl
ASSOCIATES		Max v. Zeissl 1853-1925		R. Volk H. Koenigstein A. Perutz St. Bruenauer E. Urbach and others

Fig. 1.—Personnel of dermatological clinics at Vienna. Arrows indicate academic line of descent.

small. Around 1850, only Vienna, Munich (since 1832), Würzburg (since 1849), and Berlin (since 1853) had any hospital space for skin patients. The latter three even were primarily organized for the care of venereal disease patients, and only Vienna had individual clinical services, under separate directors, for venereal and skin diseases. In those days, of course, there were no "dermatologists" in the modern sense of the word. Internists, surgeons, or men of manifold interests were in charge of the services and taught selected topics in the field of dermatology. They were more or less self-taught. They had no foundation on which to build. Worse, however, was the fact that they had to overcome prejudice and fantastic traditions before they could establish their own observations. Their microscopes were primitive and their histologic methods crude. Considering all these circumstances, it is truly difficult for us to comprehend how those men arrived at their fundamental conclusions, and we must hold great respect for their achievements.

VIENNA

The Vienna School, the first and most important among the dermatological schools in the German-speaking area, had the good fortune to be subjected to a combination of circumstances which favored its development from the outset. The Austrian capital represented an environment of immense wealth, political stability, and centralized cultural life. The founder of the school, Ferdinand von Hebra, a man of remarkable genius and character, was aware of the scientific trends of this period and applied himself diligently to the tasks before him. His close friendship and association with Rokitansky and Skoda stimulated him and gave him strength to materialize his revolutionary ideas. He was fortunate in that a great number of unusually gifted men gathered around him as pupils. As was already mentioned, he had a physical plant for his work, the facilities of the *Wiener Allegemeine Krankenhaus*, modest as they certainly were in the beginning, which gave him the opportunity to work independently. And, finally, the government recognized his achievement and did everything possible to promote his work and that of his successors.

It is not within the scope of this presentation to discuss the biography of Hebra and the personalities that constitute the Vienna School.[1] It is sufficient to mention here a few points of comparison between Vienna and other German schools.

Hebra limited his work to the pathology of the skin and was interested in the field of venereology only so far as it was directly concerned with the skin. Sigmund and Zeissl, both venereologists of note, were in charge of the venereal disease clinics which at a later date became combined venereologic-dermatological services. This separation must have been favorable to the fulfillment of Hebra's work and is a mark of distinction between his position and that of other early dermatologists, who were primarily syphilologists and secondarily dermatologists.

Another remarkable characteristic of the Vienna School was the continuity of tradition carried on through four generations, eventually becoming an integral part of all Austrian institutions of dermatological teaching. It is true that the contemporaries of Kaposi, Eduard Lipp at Graz, who later became one of the founders of the German Dermatological Society, and Eduard Lang at Innsbruck, both authorities in their field and teachers of excellent reputation, had gained recognition independently. Lang was even to be appointed the successor of Zeissl, as the head of the second clinic of syphilology at the *Wiener Allgemeine Krankenhaus*. He thus obtained a position equal in rank to that of Kaposi and Neumann, both pupils of Hebra. But, when Ehrmann succeeded Lang, the third generation of teachers consisted of disciples of Hebra in all three departments.

The advantages of such succession, or perhaps inbreeding, in academic schooling have been questioned. It has been said that the Vienna School suffered from a self-imposed isolation and a narrow-minded exclusiveness and conservatism. Such criticism was hardly justified. The first generation of Hebra's pupils showed a conspicuous independence from their master's teachings, which stressed clinical morphology. Auspitz, Hans von Hebra, and Pick were criticized for their susceptibility to external influence. Later on, Riehl, Luithlen, Kreibich, and others forcefully promoted modern dermatological thinking. Finally, the youngest generation distinguished itself in original clinical and laboratory research of the most modern type.

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Considering the fact that "golden eras" in cultural as well as political life usually do not last more than two generations, one can see that the Vienna School had done remarkably well and that the strong traditional element in its history had been advantageous rather than detrimental.

MUNICH AND WÜRZBURG

Nothing can point up the brilliant development of the Vienna School more clearly than a comparison of it with the schools at the universities of Munich and Würzburg, where separate hospital facilities existed as early as in Vienna. In Würzburg, space was set aside for skin patients under the aegis of the department of medicine. Franz von Rinecker (1811-1883) was an unusually brilliant teacher, distinguished by a broad knowledge of general medicine. In addition to internal

YEAR	CHIEF	ASSOCIATES	INDEPENDENT TEACHERS
1848	Gustav Simon (1810-1857)		
1853	Fr. W. von Baerensprung (1822-1864)	Max Burchardt (1831-1897)	
1863	Georg Lewin (1820-1896)	J. Pohl-Pinkus *Oscar Simon Wilh. Zuelzer Oscar Lassar Gustav Behrend	Since 1878 Heinr. Koebner Oscar Rosenthal Max Joseph Alfred Blaschko Edmund Saalfeld Reinhold Ledermann Ernst Kromayer
1884	Ernst Schweninger (1850-1924)	*B. Bloch C. Bruhns A. Buschke J. Heller *E. Hoffmann	
1896	Edmund Lesser (1852-1918)	Marie Kaufmann-Wolf *H. Loehe *P. Mulzer F. Pinkus *B. Spiethoff O. Sprinz Werther *Ferd. Zinsser and others	
1919	Georg Arndt (1874-1929)	*Franz Blumenthal *H. A. Gottron and others	
1933	Walther Friboes (1880-1945)		

Fig. 2.—Personnel of dermatological clinic at Berlin. Asterisks indicate directors of university departments.

medicine, he lectured on anatomy, physiology, pediatrics, history of medicine, and syphilology. In his later years, he limited his work to psychiatry and venereology. He wrote many articles on syphilis, and several of his pupils became prominent clinicians in various specialties, but there were no dermatologists among them. In 1883, after Rinecker's death, the skin department, which he had organized as a separate unit, was returned to the internists and remained there until 1909, when Karl Zieler (1874-1945), a disciple of Doutrelepont and Neisser, established a modern clinic.

In Munich, the hospital facilities for skin patients were specialized in name rather than in fact, for until 1902 diseases other than dermatological conditions and syphilis were treated there. Lindwurm (1824-1874), who headed the clinic from 1853 through 1869, was a popular teacher and distinguished himself with his studies on the infectiousness of syphilis and by performing inoculation experiments

which proved the dualism of the hard and soft chancres. His successor, Karl Posselt (1837-1916), gradually nurtured the inpatient and outpatient departments to dermatological maturity. He was a surgeon by training, but his interest in syphilis led him to specialization in that field. Although his clinical and investigative ability was outstanding, because of a deep-rooted dislike of publicity he failed to publish research data of his own. His best-known pupil was Albert Jesionek (1870-1935), later professor at Giessen, who gained renown in the field of cutaneous tuberculosis and heliotherapy. Of the other associates of Posselt, Leo Hauck was appointed professor at the Bavarian university in Erlangen, while Julius Karl Mayr and August Poehlmann continued to teach at the university of Munich. In 1915, when Leo Ritter von Zumbusch (1874-1940), a pupil of Riehl, was placed in charge of the department, the spirit and tradition of the Vienna School added new color to the dull record of the Munich clinic. His name is usually associated with his publication on "lichen albus," but he had also published studies on pustular psoriasis, acute disseminated lupus erythematosus, and other conditions. In his earlier years he investigated physiologic problems related to the skin, such as the chemistry of fat secretion and general metabolism in psoriasis. Among the pupils of Zumbusch, Kiendl (Augsburg), Moncorps (Münster), Siemens (Leyden, Netherlands), Schumacher (Königsberg), Wuerz (Munich), and Bohnstedt (Giessen) reached prominence.

BERLIN

In the northern part of Germany, Berlin had the oldest school of dermatology, which, together with its younger sister department in Breslau, did more for the development and growth of our specialty in Germany than any other school.

In 1848, Gustav Simon (1810-1857) was the newly appointed head of the syphilis section at the Charité Hospital. Since 1844, he had lectured on pathology, but with his appointment to the Charité staff he began to teach pathology and therapy of skin diseases, as well as syphilis. Previously he had shown special interest in dermatological subjects by publishing articles on the structure of condylomas and warts (1839), on pigment in the skin (1840), and on the development of hair (1841). In 1842, he gave an original description of the Demodex folliculorum. His main work, however, was published in 1848 under the title "Skin Diseases Interpreted in the Light of Anatomical Investigation." This book has retained fundamental historical importance, inasmuch as new microscopic techniques were described for the first time and its content was based on Virchow's cellular pathology. The parallel which existed between Rokitansky's influence on Hebra and Virchow's influence on Gustav Simon is unescapable and was indicative of current dermatological trends.

Unlike the Vienna School, the Berlin School lived under an unlucky star. Only 10 years after Simon had begun his teaching career, he fell ill at the age of 43. Like many other syphilologists of his time, he had infected himself with the disease; dementia paralytica developed and he died of it three years later, in 1857, leaving no associates to continue his work.

On Schoenlein's recommendation, Friedrich Wilhelm von Baerensprung (1822-1864) was appointed Simon's successor. In 1848, he had joined the medical faculty at Halle with an inaugural thesis on the cutaneous absorption of mercury. His "Essay on the Anatomy and Pathology of the Human Skin," published in the same

year, was considered one of the important contributions to the advancement of skin pathology. Soon after his appointment at Berlin in 1853, he recognized the need for a separate skin disease department, which eventually was established in 1856. Both services were placed under his direction and supplied the cases for his clinical lectures in dermatology, as well as in venereal diseases.

Baerensprung was one of the great founders of dermatology and compares well with his contemporary, Hebra. His scientific approach and his critical methods were remarkable. He was probably the first to differentiate between hard and soft chancres on clinical grounds. Of greater interest to the modern student, however, was his study on herpes zoster, which he recognized by clinical observation alone as the cutaneous manifestation of a disease involving the spinal ganglia. Later, he was able to prove this point by autopsy observations. In general, his correlation of the clinical findings with the pathology and pathogenesis impresses the reader as far advanced in comparison with the publications of his more famous contemporaries.

A short lifespan denied Baerensprung the recognition he deserved. Like his predecessor, Gustav Simon, he acquired a syphilitic infection which soon resulted in dementia paralytica. In 1863, he was forced to interrupt his work, and a year later, at the age of 42, he ended his life.

One of Baerensprung's assistants, Max Burchardt (1831-1897), achieved fame by his description of erythrasma in 1854 and the discovery of the causative fungus, a finding which his chief confirmed and later named Microsporon minutissimum. Borchardt, an army physician who worked under Baerensprung for only a limited period, later specialized in ophthalmology.

At the time of Baerensprung's retirement, there was no dermatologist with sufficient experience and academic status to assume charge of the department. Georg Lewin (1820-1896), a young internist with a special interest in diseases of the chest and upper respiratory tract, was appointed to that position one year after he had joined the medical faculty at Berlin. His teaching experience consisted mainly of a course in laryngoscopy, the first of its kind in Berlin. He adapted himself brilliantly, however, to his new task, and during the long years of his teaching career he wrote a number of monographic articles on Addison's disease, unilateral facial atrophy, scleroderma, syphilitic myositis, and many other syphilological subjects. He originated the intramuscular injection therapy of mercury bichloride, which he considered a more advantageous type of antisyphilitic treatment than the percutaneous method.

His teaching was ably supported by several associates, among whom Oscar Simon (1845-1882) and Oscar Lassar (1849-1907) were outstanding. Simon distinguished himself later at Breslau as successor to Koebner. Lassar, whose name is familiar to us through common usage of the paste designed by him, had gained importance as the founder of the *Dermatologische Zeitschift*, now carrying on as the international journal *Dermatologica*. He also organized an independent private dermatological clinic in Berlin, where he trained young physicians and which had a world-wide reputation.

In 1884, the apparently prosperous continuity of the Berlin School suffered a new unfortunate interruption. For no apparent reason, a dermatological section with 20 beds was segregated and placed under the direction of Ernst Schweninger (1850-1924), while Lewin continued to head the larger syphilis clinic. Schweninger was a pathologist by training and had no particular qualifications for the position

of head of a dermatological section, except that he was the personal friend of and physician to the chancellor Bismarck, who was then the uncontested political master of central Europe. The protest of the medical faculty against this appointment was of no avail. The separation of the clinics, which, of course, created many tensions and interdepartmental feuds, lasted 18 years. Schweninger finally preferred to exchange his place for a professorship in general pathology and the history of medicine.

Lewin never lived to see the reunification of his clinic. He died in 1896, and Edmund Lesser (1852-1918) was called to succeed him, at first as the head of the syphilis clinic and in 1902, after Schweninger's resignation, as the director of the reunited departments of skin and venereal diseases. Thus, for the first time in its existence—indeed, 50 years later than the school in Vienna—the Berlin School achieved the stability which is a prerequisite for the successful development of a research or teaching institution.

Lesser became interested in dermatology shortly after his graduation at the age of 24, probably under the influence of Hebra, whom he heard during a visit to Vienna. After his return to Breslau, his alma mater, he worked under Oscar Simon, whom Hebra had judged one of the best dermatologists of the time. Simon recognized Lesser's ability early, and during his own critical illness left the direction of his clinic and his teaching obligation to his young assistant. As a lecturer on skin diseases in Leipzig and as professor of dermatology at Bern, Switzerland, Lesser had proved himself an outstanding teacher, investigator, and organizer. His textbook on skin and venereal diseases, which was and remained popular for years after his death, gained him early literary recognition. His appointment was a fortunate one, for his tact and cautious reserve made it possible for him to overcome the strife within the clinic which had existed during the Schweninger interlude. His reorganization of the department with enlarged hospital facilities, with an outpatient service, and with a section for actinotherapy, caused it to become a model institution of its time. Lesser disliked publicity; when his clinic stood in the limelight of public attention with the discovery of the Spirochaeta pallida, reported by Schaudinn and Erich Hoffmann, his name as one of the organizers of the project hardly appeared in the literature.

The number and names of Lesser's disciples, many of whom contributed to German dermatology during its golden age, give the most eloquent testimony of his ability as a teacher: Arndt, Bloch, Bruhns, Heller, Erich Hoffman, Loehe, Mulzer, Pinkus, Spiethoff, Sprinz, Ferdinand Zinsser, and others. Most of these men distinguished themselves later as academic teachers either at university clinics or at large municipal hospitals, which were often better equipped for postgraduate training than were the university departments. Although Lesser did not describe any new dermatological entities or create new theoretical concepts, his historical significance rests on this aggregation of outstanding pupils, a merit which he shared with his contemporary Neisser in Breslau, who even surpassed him in this respect.

After Lesser's death in 1918, it was only natural that one of his associates be called to succeed him. Georg Arndt (1874-1929) was chosen. Because of the unfavorable outcome of the first World War for Germany, he had lost his clinic at the university in Strasbourg, where he had been professor of dermatology since 1916. It is with some nostalgic affection that I speak of him, since he gave me, a young student at the medical school in Berlin, my first taste of dermatology. He

impressed me not so much with his profound knowledge or his conscientious teaching, most of which I did not understand in those days, but with his sincerity, honesty, and modesty. Arndt was the last of the great morphologists, willing to accept new functional concepts when proved and substantiated by facts, but ill-disposed toward scientific speculation in any form. With the greatest care and with utter disregard for time, he tried to point out to his students diagnostic characteristics and their correlation with the histologic findings. His detailed knowledge of dermatology was acquired during long years of travel and study at the leading schools of his time. In his youth, when he was forced to interrupt his studies of surgery and pathology because of poor health, he visited Switzerland and met Oltramare in Geneva, who awakened his interest in dermatology. He continued the study of the subject in London and Paris. After Paris, he worked in Bern under Jadassohn

YEAR	CHIEF	ASSOCIATES	
1877	Heinrich Koebner (1838-1904)		
1878	Oscar Simon (1845-1882)	*Albert Neisser—Leipzig & Breslau *Edmund Lesser—Leipzig & Berlin *Eduard Arning—Hamburg	
1882	Albert Neisser (1855-1916)	C. Bruck—Altona A. Buschke—Berlin *K. Herxheimer—Frankfurt *E. Jacobi—Freiburg *J. Jadassohn—Bern & Breslau F. Juliusberg—Braunschweig *V. Klingmueller—Kiel E. Kuznitzky—Breslau R. Ledermann—Berlin L. Leven—Elberfeld	*K. Zieler—Wuerzburg *P. Linser—Tuebingen E. Meirowsky—Cologne & Indianapolis W. Pick—Prague F. Pinkus—Berlin *W. Scholtz—Koenigsberg *A. Stuehmer—Muenster & Freiburg C. Touton—Wiesbaden F. Veiel—Cannstatt and others
1916	Joseph Jadassohn (1863-1936)	At Bern *G. Arndt *Bruno Bloch F. Juliusberg *F. Lewandowsky F. Pinkus *O. Naegeli F. Schultz R. O. Stein	At Breslau H. Biberstein St. Epstein Wilh. Frei W. Freudenthal R. Habermann *W. Jadassohn *Max Jessner C. Lennhoff H. Mertenstein Herm. Pinkus *H. W. Siemens and others
1931	Max Jessner		

Fig. 3.—Personnel of dermatological clinic at Breslau. Asterisks indicate later directors of university departments.

until 1906, when he joined Lesser's staff in Berlin. Shortly before the outbreak of the first World War, he visited the United States to acquaint himself with American schools and methods.

Arndt's publications on parapsoriasis, pseudopelade, granuloma annulare, lichen nitidus, sporotrichosis, Hodgkin's disease, and leukemic dermatoses were masterpieces of observation. He was extremely critical of his own work and demanded the same high standards from his associates. A legend is told that he retained the manuscripts of members of his staff in his desk for a year. If, after this lapse of time, the author still considered the contribution worth while, he was allowed to publish it. Naturally, this policy of retarded progress was not popular with the younger set of ambitious associates who thought their careers jeopardized and who often left the clinic sooner than would have been desirable for the interests of the school.

Arndt died in 1929, at the age of 55, leaving the clinic to Franz Blumenthal, who directed the department until 1933. At this time Walther Friboes (1880-1945), then professor in Rostock and a former pupil of Lesser and Erich Hoffmann, received the appointment. Arndt's assistant, H. A. Gottron, who distinguished himself in the field of metabolic and circulatory dermatoses, is now professor at Tübingen.

BRESLAU

Although the dermatological clinic in Breslau had a much later start than its sister institutions in Vienna and Berlin, it grew rapidly, and within a quarter of a century it had surpassed all others in importance and was able to assume the leadership of German dermatology.

The founder of the clinic was Heinrich Koebner (1838-1904), a true pioneer in the field, who deserves a much more prominent place of honor in the annals of medicine than is granted him. Born in Breslau and educated there and in Berlin, Koebner was recognized by his teachers as an unusually gifted student. After his graduation in 1859, he visited Vienna, where, under the influence of Hebra, he chose dermatology as his special field. He continued his studies in Paris, and, on his return to Breslau in 1861, he established a private clinic for skin diseases and syphilis. It was during this time that he first reported the fungous nature of sycosis parasitica, a causation then denied by Hebra. The publication of this work together with other clinical and experimental data effected his admission to the medical faculty at Breslau in 1869. Soon after his academic career began, he envisioned the organization of a university clinic for dermatology and venereology and fought for five years virtually singlehandedly, often in opposition to the medical faculty, to attain this goal. The year 1876 finally brought him success. A new department with hospital facilities was organized and placed under his direction. But barely had he begun to reap the fruit of his labor when illness tragically interrupted his work and forced him to withdraw from his position. In the middle of a lecture to his students one day, he suddenly became unable to speak. His indomitable mind, however, did not allow him to idle long. As soon as he recovered from his illness, he moved to Berlin, where, in 1877, he again founded a private clinic, the facilities of which he used for his lectures to postgraduate students.

Koebner's name is best known in this country for the phenomenon bearing it, but, in addition to the fundamental papers previously mentioned, he wrote prolifically on such subjects as lichen ruber, mycosis fungoides, sarcoma, pemphigus vegetans, lepra, and syphilis. Koebner was not one to rush pen to paper, as his pupil Wechselmann reported. He worked up his projects for years and controlled his observations and experiments time and again before he considered them ready for publication. Though he was not inclined to speculative deductions, he had sufficient imagination to recognize causal relationships and to prove their existence, as he demonstrated in his report on drug eruptions.

Koebner's successor, Oscar Simon (1845-1882), who transferred from the University of Berlin, had a similarly fateful career. After postgraduate studies in Vienna under Hebra, Sigmund, and Zeissl—which were interrupted by military service during the Franco-Prussian war in 1870-1871—he was admitted to the faculty at Berlin, where he taught under Lewin for nearly six years. In 1878, only 33 years of age and already afflicted with a fatal disease, Simon assumed charge of

Koebner's young clinic, which was still suffering growing pains. Excessive administrative duties, together with his teaching obligations and his slowing advancing infirmity, limited his literary production. His main work "The Localization of Cutaneous Diseases, Histologically and Clinically Discussed," as well as his study on molluscum contagiosum, was written before his Breslau days. Later publications deal with multiple gangrene of the skin, prurigo, taches bleuâtres, and other subjects.

In 1882, only four years after Simon had begun his promising activity at Breslau, he died of gastric cancer. His disciple and successor, Albert Neisser (1855-1916), praised his work and his unusual ability as an organizer, teacher, and physician. Concerning the young clinic, he wrote: "Koebner had planted the sprig. But had not Simon, the expert gardener, cared for the young plant, it would not have grown to be the strong tree which was entrusted to me."

With Neisser's return from Leipzig, where he had lectured for only two years, the Breslau clinic entered its golden age which was to last for about 50 years. The setting was ideal: a new, but well-established clinic, the opening of the bacteriological era, and, last but not least, a young, energetic, and ambitious department head, well prepared for leadership.

After his schooling at Breslau, Berlin, and Erlangen, Neisser, then only 23 years old, had started his brilliant career at Oscar Simon's clinic. Within a year, he reported his discovery of the Gonococcus. During his teaching period in Leipzig from 1880-1882, he published two excellent studies on the etiology of lepra and the treatment of syphilis. At the age of 27, he was named professor of dermatology at Breslau, ready to begin the exceptionally successful period of dermatological research and teaching which was to last 34 years. He became the outstanding German dermatologist of the bacteriological era, just as Hebra was the protagonist of the pathologicoanatomical period in the history of dermatology. Likewise, as Hebra rallied gifted scholars who contributed to the development of his school, so Neisser attracted numerous disciples who, inspired by their teacher, supported his work and carried the spirit and content of his teaching to their future fields of activity. It is impossible to name them all here. Only some who distinguished themselves as teachers or research men may be mentioned:

Arning, Hamburg	Bettmann, Heidelberg
Bruck, Altona	Buschke, Berlin
Epstein, Nürnberg	Galewsky, Dresden
Harttung, Breslau	Herxheimer, Frankfurt
Jacobi, Freiburg	Jadassohn, Bern and Breslau
Juliusberg, Braunschweig	Klingmueller, Kiel
Kuznitzky, Breslau	Linser, Tübingen
Lipschuetz, Vienna	Melrowsky, Cologne and Indianapolis
W. Pick, Prague	F. Pinkus, Berlin
Scholtz, Königsberg	Stuehmer, Münster and Freiburg
Touton, Wiesbaden	F. Veiel, Gannstatt
Winternitz, Prague	Zieler, Würzburg

In this country, Neisser's name is usually associated with the discovery of the Gonococcus, but from the viewpoint of the historian one should probably regard this achievement as the least important of his contributions. The wide range of his knowledge and his versatility in its application were astounding. In accordance with the trends of his time, he was mainly interested in tuberculosis, lepra, and the venereal diseases. There was hardly a dermatological topic, however, on which he or a member of his staff had not reported at some time or another. His disciple and

later successor, Jadassohn, regretted that many of Neisser's suggestions to the members of his staff could not have been worked up, but there were just too many of them.

Beyond the varied activities within his own clinic, Neisser promoted the interest of German dermatology more than any teacher before or after him. In public statements, as well as in his communications with governmental agencies, he did not tire of stressing the importance of dermatological teaching and requesting the organization of specialized clinics at all universities. In 1888, together with Eduard Lipp, of Graz, and F. J. Pick, of Prague, he founded the German Dermatological Society, and in 1902 he assisted in the establishment of the German Society for Combating Venereal Disease, both of which helped materially in giving dermatology increased recognition in the German-language area. Finally, he was co-editor of the periodical published by the last-mentioned society, as well as of the German

YEAR	CHIEF	ASSOCIATES
1882	Joseph Doutrelepont (1834-1918)	Joh. Fabry—Dortmund *Carl Grouven—Halle J. F. B. Hahn—Bremen Joh. Sowade—Halle *Max Wolters—Rostock *Karl Zieler—Wuerzburg and others
1910	Erich Hoffmann (born 1868)	*Walther Fribocs—Greifswald & Berlin Rud. Habermann—Hamburg Wilh. Heuck—Munich Edm. Hofmann—Frankfurt/Main & Kassel Alois Memmesheimer—Essen *G. A. Rost—Freiburg & Berlin *Alfr. Ruete—Marburg *H. Th. Schreus—Duesseldorf *Emil Zurhelle—Groningen/Holland and others
1933	Otto Gruetz (born 1886)	

Fig. 4.—Personnel of dermatological clinic at Bonn. Asterisks indicate later directors of university departments.

Archiv für Dermatologie und Syphilis. No wonder then that the beginning of the 20th century Breslau had become the capital of German dermatology.

When Neisser died in 1916 it must have appeared difficult to fill the vacancy with a worthy successor, but it was the good fortune of German dermatology that Joseph Jadassohn (1863-1936) was avaiiable and chosen. From Judassohn's biography, presented here by his pupils and personal friends,[2] we have learned of his achievements and human qualities. It is obvious that a man of such stature not only continued and fulfilled the work of his predecessor but also led his contemporaries into the new era of functional dermatology, the study of which has remained our concern up to the present. During his teaching career, he trained numerous pupils in Bern, as well as in Breslau, many becoming gifted teachers and investigators in their own right. Some died before Jadassohn, such as Lewandow-

2. Sulzberger, M. B., and Jessner, M.: Joseph Jadassohn, read before the tenth meeting of the American Academy of Dermatology & Syphilology, Chicago, Dec. 12, 1951.

sky in Basel, Arndt in Berlin, and Bloch in Zurich. Others carried on the work of their great master; among them were F. Juliusberg, Frei, Jessner, his son Werner Jadassohn, Epstein, Walter Freudenthal, and Hermann Pinkus.

BONN

The West German School in Bonn on the Rhine, the third in Prussia, originated not unlike Breslau, its great counterpart in the east, through the personal initiative of a single person, Joseph Doutrelepont (1834-1918). In the middle of the 19th century, Bonn was a small romantic university town of about 35,000 population, with more than a thousand years of tradition, but without political or economic importance. The medical faculty had suffered from inadequate hospital facilities since the founding of the university after the Napoleonic wars. Shortly before the building of new hospitals was begun in 1870, Doutrelepont had joined the medical faculty as a teacher in surgery and ophthalmology. In Bonn in those days, venereal and cutaneous diseases were considered a part of the surgical domain. Doutrelepont had lectured on syphilis for several years, but not until 1876, that is, five years after he was promoted to a professorship in surgery, did he begin to lecture on diseases of the skin. From this point on, he became increasingly interested in dermatology, and in 1879, as the university had no facility for clinical work in dermatology, he opened a private clinic for treatment of skin disease patients while he continued his other surgical duties. At the same time, however, he recognized the need for a specialized university clinic and urgently requested the organization of such an institution. Circumstances favored his planning. The head of the department of surgery, as well as members of the medical faculty, supported Doutrelepont's project. In 1882, the same year that Neisser became head of the Breslau school, a clinic with 60 beds and room for an outpatient service was built and placed under the direction of Doutrelepont, who by that time was almost 50 years of age, nearly twice as old as his contemporary Neisser. He had had no training in dermatology, and whatever he had learned he had acquired through his own observations and study of the literature; yet he became an expert in the field while he continued to pursue his first-chosen specialty, surgery. In the light of these facts, Doutrelepont's accomplishments during the following 28 years deserve special recognition. His transplantation experiments of cancer were probably among the first performed. After Koch's discovery of the tubercle bacillus, Doutrelepont was among the first to demonstrate the organism in lupus lesions, a relationship which was much disputed at this time and long denied by the leaders of the Vienna School. Later he proved the presence of spirochetes in late syphilitic lesions. He furthermore reported on his studies of lepra, rhinoscleroma, sycosis parasitica, pityriasis rubra, mycosis fungoides, and other entities.

At the time of his retirement, his clinic had become one of the best organized institutions for dermatological teaching and research in Germany, well equipped with a large library, laboratory, and facilities for radiation therapy. His associates, Wolters, later at Rostock, Grouven at Halle, and Zieler at Würzburg, obtained leading positions at other universities, while others, for instance, Hahn at Bremen, Fabry at Dortmund, and Heuck at Munich, directed large municipal hospital departments.

In 1910 Doutrelepont retired and was succeeded by Ehrich Hoffmann, who had received his dermatological training under Lesser in Berlin and who, prior to his

appointment at Bonn, was professor of dermatology at the university at Halle. With Hoffmann, the traditions and teachings of the Berlin clinic were brought to Bonn, but so thoroughly blended with the local tradition that one is justified in speaking of the Bonn School as a separate unit.

The nature of Hoffmann's lifework was determined by his early interest in syphilis and by his appointment to the group of scientists who were assigned to investigate the etiology of this disease. Their studies culminated in the discovery of the Spirochaeta pallida in 1905, as described in the famous publications by Schaudinn, the zoologist, and Hoffmann, the clinician. The new vistas for research opened by this discovery were extensively explored by Hoffmann, and the clinic in Bonn became a center for investigative syphilology. All phases of clinical and experimental syphilis were explored. A special office for epidemiologic studies and treatment control was established. A therapeutic system, publicized under the heading "combined-maximal-early treatment," was developed. Perhaps too rigid in its general application, it had the advantage of relatively short treatment periods and optimal results during the early phase of the disease.

Hoffmann, however, never lost sight of dermatological problems, as his numerous publications prove. He was an excellent diagnostician whose mastery could be recognized by his associates during his daily visits in the wards and in the outpatient department. The importance of dermatological therapy was stressed in his desire to preserve the clinic's reputation as a leading treatment center. Following the modern trend toward functional dermatology, he introduced the concept of esophylaxis, by which he meant the physiologic task of the skin to secure inward protection of the human organism as exemplified in the heliotherapy of tuberculosis and the immunological reactions of the skin in exanthematous eruptions.

Hoffmann retired from office in 1933, after he had demonstrated his characteristic sincerity and courage by risking his personal freedom and life in public objections to the acts of National Socialism.

Among his pupils who distinguished themselves were Rost at Freiburg and Berlin, Frieboes at Rostock and Berlin, Ruete at Marburg, Schreus at Düsseldorf, Zurhelle at Groningen, Habermann at Hamburg, Memmesheimer at Essen, and others.

LATER SCHOOLS

The clinic at Strasbourg, though organized relatively early, in 1886, had no chance to develop a school because of the change from German sovereignty to French in 1918. Alfred Wolff (1850-1916), an excellent dermatologist, author of a textbook, and a contributor to Mraček's handbook, headed the clinic during the greatest part of its existence under German administration. Arndt directed it for only two years before the school passed into French leadership under Pautrier. The German dermatologists Ruete at Marburg, Mulzer at Hamburg, Gutmann at Wiesbaden, and others received their training partly at the Strasbourg school.

With the beginning of the 20th century, the importance of and the need for specialized dermatological training was generally recognized, and other medical schools established professorships and supplied hospital space and teaching facilities for dermatological clinics. At times the immediate reasons precipitating such steps were rather odd. In Leipzig, for example, the skin department was eventually organized because Thiersch, the famous surgeon, would accept his appointment

at this university only if the syphilis section was separated from the surgical clinic. In 1896, Riehl, a disciple of Kaposi, was called from Vienna to become the first professor of dermatology at Leipzig. Under his masterful leadership, the school got off to a good start. When Riehl returned from Leipzig to Vienna to accept the honored appointment as the successor to Kaposi in 1902, Rille, a student of von Neumann, took over the reins and maintained the traditions of the Vienna School.

In Kiel on the Baltic coast, the internist Quincke was interested in dermatological problems at the end of the 19th century. His publications on acute circumscribed edema, on the various forms of the Achorion group, and on eczema belong to the classics in dermatological literature. It is significant that he became a member of the German Dermatological Society and a co-editor of Unna's *Monatsheft für praktische Dermatologie*. As late as 1902, Ernst von Duering (1858-1944) was called to establish a university clinic for skin and venereal diseases. This capable, but temperamental, former assistant of Unna, according to Delbanco his ablest student, had achieved professional eminence as an advisor to the government in Turkey, where he was greatly honored for his successful work. When he arrived in Kiel to take up his position, there was no room for him. Several months later, the basement of a private home was placed at his disposal, and two more years passed before he could obtain a small hospital section with 26 beds. Finally, in 1906, von Duering grew tired of the bickering with the bureaucratic administration in Berlin, withdrew from office, and requested his discharge from government service. His successor, Victor Klingmueller (1870-1942), an associate of Neisser in Breslau, must have profited from Duering's action, for he succeeded in organizing a clinic which received equal prominence with the Finsen Institute in Copenhagen for the care of lupus. Well equipped for the various types of actinic therapy, Klingmueller's department published a series of articles dealing with research in radiation, and his associates Friedrich Bering, later at Cologne, Hans Meyer, of Bremen, and G. A. Rost, of Freiburg and Berlin, became leaders in this branch of dermatology. Other pupils, such as Hans Ritter, of Hamburg, Gustav Stuemke, of Hannover, and Otto Gruetz of Bonn, also attained prominent positions.

The group of university clinics in the southwest of Germany, Freiburg, Tübingen, and Frankfurt, rapidly developed a brilliant reputation under the direction of Neisser's disciples. In Freiburg, Eduard Jacobi (1862-1915), whose name we associate with the famous atlas of skin diseases and with poikiloderma atrophicans vasculare, was succeeded by Georg-Alexander Rost, now in Berlin, whose pupils Keller, of Aachen, and Stuehmer, of Freiburg, achieved eminence. Another of his pupils, Marchionini, who distinguished himself early by his work with Heinrich Schade on the "acid coating" of the skin, spent the second World War in Turkey but returned to Germany after the surrender and has now succeeded Zumbusch in Munich. His most recent achievement is the revival of the German Society of Dermatology, which elected him its president. The school in Tübingen was under the direction of Paul Linser for many years and is now presided over by H. A. Gottron, a former assistant of Arndt, who has done original work in the field of metabolic and circulatory dermatoses.

The school in Frankfurt-am-Main stemmed from a large department for skin patients at the Municipal Hospital Sachsenhausen. Its director, Karl Herxheimer, continued as professor of dermatology when the university of Frankfurt was founded in 1914. Herxheimer's authorship of the descriptions of epidermal spirals,

of the increase of syphilitic symptoms following initiation of therapy, and of acrodermatitis chronica atrophicans is well known in this country. In the year of his retirement, 1930, Oscar Gans, the pupil of Siegfried Bettmann in Heidelberg, was appointed to the professorship in Frankfurt. The achievements of Gans in the field of histopathology of the skin are common knowledge to the American dermatologist.

Thus, after the first World War, dermatological clinics had been instituted at all German universities, with Greifswald as the last organized under Walther Schoenfeld, a pupil of Zieler in Würzburg. Schoenfeld, who has distinguished himself as a historian of German dermatology, has recently gained historical importance in his own right as one of the few who after the collapse of Nazi might in Germany rallied the survivors to reorganize and revive German dermatology. In 1929, the roster of German dermatologists listed 24 university clinics within the former area of the Reich, in addition to those in the German-language schools of Austria, Switzerland, and Czechoslovakia, as well as the numerous dermatological services in municipal hospitals where young dermatologists could also be trained.

CONCLUSION

In finishing this review, in which the subject could be treated only in a most superficial and incomplete manner, I ask your indulgence if important personalities and events were omitted or inadequately discussed. By and large, the report ends with the year 1933, that fateful year when academic freedom in Germany was utterly destroyed by National Socialism. To survey the 12 years of dictatorial misrule with any fair degree of objectivity is impossible at this time. When the dictatorship collapsed, there was nothing left but ruin and chaos. Since then, signs of a resurrection of German dermatology have appeared. A new generation is working intently to prove itself worthy of the old traditions and to uphold academic standards of freedom, honor, and decency. If history will grant German science the opportunity for a peaceful development, we may be certain that it will further contribute its share to the progress of dermatology and the welfare of mankind.

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ORIGINAL DESCRIPTION OF LUPUS ERYTHEMATOSUS

EMANUEL GAHAN, M.D.
NEW YORK

IN FRENCH dermatologic literature, lupus vulgaris is still sometimes referred to as *lupus de Willan* and lupus erythematosus as *lupus de Cazenave*. Although Biett had described one clinical form of the latter dermatosis in 1828 as *erytheme centrifuge* and Hebra another form in 1845 as *seborrhea congestiva*, it was Cazenave who, just about one hundred years ago, gave the first full account of several varieties of the chronic form and who gave the entity its present name.

The original description of the disease appeared as a clinical lesson given to medical students at the Hôpital St. Louis in Paris. It was contained in the August, 1851, number of the *Annales des maladies de la peau et de la syphilis*, the first dermatologic journal in French, which Cazenave himself had founded several years earlier. It is indeed interesting to note how accurate some of his observations in this first description were.

The author presented a 38-year-old man who had an eruption of the face. He called this eruption "lupus erythematosus," which he defined as a little-known disease associated with general health, causing neither ulcers nor crusts, producing thinning of the skin, and leaving indelible scars. The three important points in the diagnosis were (1) redness, (2) erosion of the skin without ulceration (the word *usure* appeared in the original French), and (3) appearance of the lesions in a variety of different clinical aspects. The author thought that it was seen more frequently among people who worked in proximity to ovens or out in the open air. Follicular plugging was also observed; this was called *pointillé* in the description, but the association with the hair follicle was not mentioned. The clinical resemblance to frostbite was noted, and Cazenave thought that many cases were incorrectly diagnosed as such. The topography was given with a fair degree of accuracy; according to the description, the lesions were seen almost exclusively on the face but also occasionally on the scalp and less commonly on the neck and hands. The disease was considered a variety of lupus (i. e., lupus vulgaris), but, unlike that dermatosis, lupus erythematosus was seen most frequently in mature years rather than in early life, and it had no effect on the general condition of the patient. No mention was made of the acute disseminated form of lupus erythematosus; this was not described until 1872 by Kaposi.

The first textbook account of the disease appeared in 1853 in Maurice Chausit's *Traité elementaire des maladies de la peau*. The author, a pupil of Cazenave's, elaborated on the original description that his teacher had given. The following year the textbook of Devergie appeared; it contained a description of *herpès crétacé*,

From the Department of Dermatology and Syphilology, New York University Post-Graduate Medical School and the Service of Dermatology and Syphilology, Bellevue Hospital.

a term still sometimes used in French to denote the hypertrophic chronic discoid form, but there was no mention of lupus erythematosus. Bazin's *Leçons cliniques*, in 1860, did not mention it at all.

In English-speaking countries the new entity gained immediate recognition. The third edition of *On Diseases of the Skin*, by Erasmus Wilson, appeared in England in 1851 and made the following mention of the new disease which had just been described:

> Cazenave mentions a new variety of lupus which he calls lupus erythematosus. Cazenave is right in distinguishing this form of cutaneous disease, but whether he is equally so in placing it in the same group with lupus is a question yet to be determined.

The fourth edition of the same textbook, in 1857, contained a complete description. Lupus lesions were divided into three varieties. There were those in which there was destruction by ulceration; those in which there was no destruction by ulceration, and a third form, in which there was destruction of the skin but no ulceration and no tuberculous thickening, the only other outward sign of the disease, besides the atrophy, being erythema. According to Wilson it was doubtful that this third form, lupus erythematosus, really belonged to the lupus group.

12 W. 44th St. (18).

SECONDARY ERUPTIVE XANTHOMATOSIS DUE TO MYXEDEMA

A Genetic and Metabolic Study

ARTHUR C. CURTIS, M.D.
ANN ARBOR, MICH.
AND
HOYT C. BLAYLOCK, M.D.
WICHITA, KAN.

THE FREQUENT association of hypercholesteremia with hypothyroidism and particularly myxedema allows one to postulate that a secondary eruptive form of xanthomatosis should occasionally occur in either of these conditions. Actually, only three such reports have been published in which the occurrence of this type of xanthomatosis with either of these diseases has been noted.[1] This paucity of reports makes one wonder whether the hypercholesteremia alone is the deciding factor in the formation of the secondary eruptive xanthomatosis in myxedema or whether some other related but as yet undisclosed abnormality, such as essential familial hypercholesteremia, acting as an additive factor, precipitates this eruption. In none of the three previously reported patients had a pedigree for essential familial hypercholesteremia been reported. One of the problems then to be answered is to ascertain whether xanthomatosis associated with myxedema is due to the summation effect of the hypercholesteremia due to the myxedema and that present in primary essential familial hypercholesteremia. The following case is reported to answer the latter problem and presents another example of myxedema and secondary eruptive xanthomatosis.

REPORT OF A CASE

M. K., a 38-year-old farmer, was first seen in the department of dermatology at the University of Michigan Hospital, Dec. 12, 1949. His presenting complaint was an eruption of his arms, legs, and trunk of two months' duration (Fig. 1). These yellowish lesions were asymptomatic, but in the past year he had noticed fatigability, listlessness, inability to concentrate, weight gain, increased sensitivity to cold, loss of hair and libido, and a dry skin. His past history was noncontributory except for an episode of jaundice, chills, and fever three years before the onset of the present illness. The patient's wife and two children had jaundice at the same time. The patient's father had arteriosclerosis, and his mother had cholelithiasis.

From the Department of Dermatology and Syphilology, University of Michigan Medical School.

1. Christie, J. F.; Lyall, A.; Anderson, T. E.: Case of Xanthoma Multiplex Associated with Hypothyroidism, Brit. J. Dermat. **42**:429, 1930. Sweitzer, S. E., and Winer, L. H.: Xanthoma Tuberosum and Myxedema, Arch. Dermat. & Syph. **42**:419, 1940. Craig, L. S.; Lisser, H., and Soley, M. H.: Report of 2 Cases of Myxedema with Extreme Hypercholesteremia: One complicated by Xanthoma Tuberosum, J. Clin. Endocrinol. **4**:12, 1944.

The physical examination on Dec. 12 showed a moderately obese white man who weighed 204 lb. (92.6 kg.). He answered questions slowly and apathetically; his voice was hoarse, and his skin was dry and cool. The skin about the eyelids was puffy. Over the elbows, knees, shoulders, and buttocks there were many grouped papules, yellow-orange in color and measuring 1 to 3 mm. in diameter. The lesions were firm, nonpainful, and not fixed to underlying tissue. The mucous membranes were uninvolved. The scalp hair was dry and the body hair scanty, especially on the arms and legs. Findings on a funduscopic examination were negative. The blood pressure was 118 systolic and 70 diastolic in the right arm. The pulse rate was 72 and regular. The heart was not enlarged, and there were no murmurs. The liver and spleen were not palpable. Examination of the extremities disclosed no abnormalities. There were no palpable masses over the tendons, and the reflexes were physiological.

Laboratory Reports.—The urine was clear, acid in reaction, and free of albumin and sugar. The microscopic examination showed 0 to 2 red blood cells and 0 to 2 white blood cells per high power field.

Fig. 1.—Myxedema and associated cutaneous xanthoma of the elbow.

The hemoglobin content of the blood was 80%, the red cells 4,700,000 and the white cells 11,500 per cubic millimeter. The differential blood count was within normal limits. The sedimentation rate was 28 mm. per hour (Westergren method); results of a battery of liver tests were normal. Findings on an x-ray examination of the chest were normal. A routine Kahn serological test for syphilis was negative. The basal metabolic rate was —32%.

Results of chemical studies on the blood were as follows: The fasting blood sugar level was 72 mg. per 100 cc. The total blood cholesterol was 568 mg. per 100 cc. (Schoenheimer-Sperry method—normal range, 120 to 210 mg. per 100 cc.); free cholesterol, 177 mg. (normal range, 60 mg.); cholesterol esters, 391 mg. (normal range, 170 mg.), total fatty acids, 732.7 mg. (normal range, 190-450 mg.), and lipid phosphorus, 13.8 mg. (normal range, 6 to 10 mg.). The lecithin was estimated at 345 mg. per 100 cc. (normal range, 150 to 230 mg.).

A biopsy specimen taken from the skin of the left elbow showed slight atrophy of the epidermis with hyperkeratosis. The corium had marked edema with swelling and fragmentation of the collagen fibers. The infiltrate in the corium consisted of collections of histiocytes, foam cells, and a few lymphocytes (Fig. 2).

Pedigree.—The patient was seen in the heredity clinic of the University Hospital, where the pedigree on his family for three generations was established. This pedigree proved that primary essential familial hypercholesteremia was not present. The patient was the propositus in this pedigree[2] (Fig. 3).

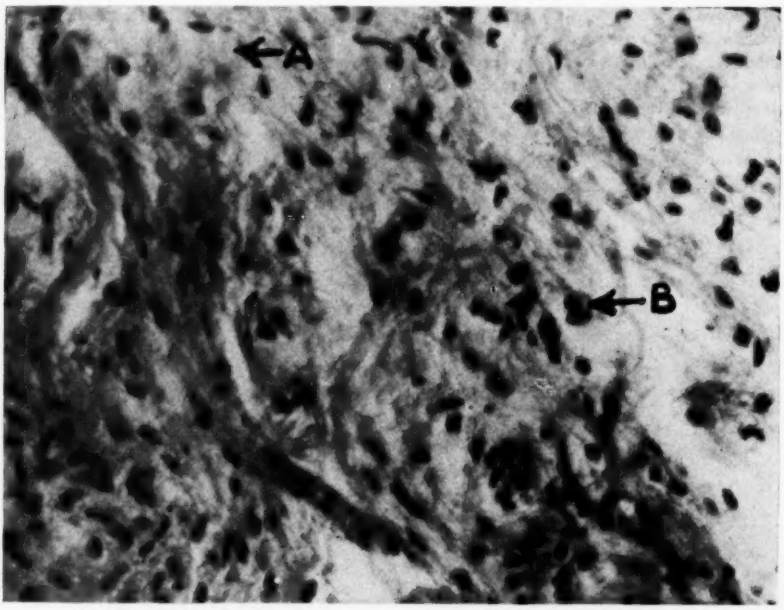

Fig. 2.—High power photomicrograph of a section from the left elbow, showing swelling and fragmentation of the collagen fibers (*A*) and foam cells (*B*); hematoxylin and eosin.

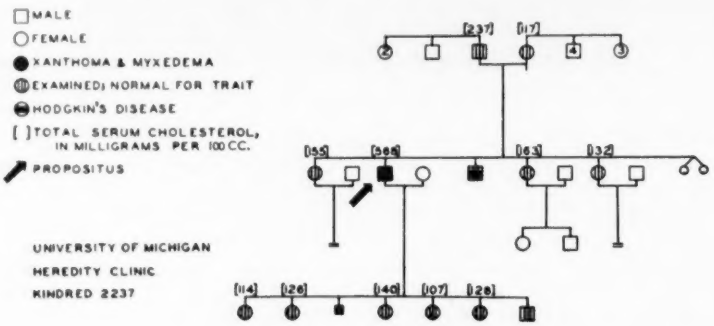

Fig. 3.—Kindred No. 2237.

Course.—The patient was given an average of 2 grains (0.130 gm.) of desiccated thyroid daily. The xanthomatous lesions became noticeably smaller. The patient's general health improved, his lassitude decreased, and his speech became more fluent. The basal metabolic

2. Dr. J. V. Neel, of the Heredity Clinic, University of Michigan Hospital, and Dr. Frank Crowe of the Department of Dermatology, aided in establishing Kindred No. 2237.

rate improved over a period of four months' observation from the original —32 to —18%. The total blood cholesterol decreased during the same period from the original 568 mg. per 100 cc. to 320 mg.; the free cholesterol fell from 177 to 103 mg., and the cholesterol esters decreased from 391 to 127 mg. Two years later the xanthomatous lesions had all disappeared except for three or four yellowish papules over each elbow (Fig. 4). The serum lipid values were still slightly above normal. The total serum cholesterol was 393 mg. per 100 cc. The free serum cholesterol was now 309 mg. and the cholesterol esters 84 mg. The serum lecithin was 32.4 mg. and the serum phosphorus 2.6 mg. The patient still had clinical findings of mild hypothyroidism and a basal metabolic rate of —15%.

CLASSIFICATION OF XANTHOMATOUS DISEASE

Thannhauser,[3] in his classification of the various diseases exhibiting xanthomatous formation, lists four main groups: (1) primary familial essential xanthomatosis of the hypercholesteremic type; (2) primary essential xanthomatosis of the

Fig. 4.—Myxedema and associated cutaneous xanthoma two years following therapy.

normocholesteremic type; (3) secondary eruptive xanthomatosis associated with hyperlipemia; (4) localized xanthoma associated with inflammatory tissue and true tumors.

To classify a xanthomatous eruption within one of the above four groups, a careful study must be made to rule out primary familial essential xanthomatosis of the hypercholesteremic type. Wilkinson, Hand, and Fliegelman [4] have shown the increased blood cholesterol in this group to be genetically a dominant. It was further found that xanthoma tuberosum and/or tendinosum represents the homozygous abnormal, whereas hypercholesteremia without xanthomatosis represents the heterozygous abnormal. This type of inheritance is known as an incomplete dominant because the severity of the condition is less in the heterozygote than in the homozygote.

3. Thannhauser, S. J., and Schmidt, G.: Lipins and Lipidoses, Physiol. Rev. **26**:296, 1946.

4. Wilkinson, C. F.; Hand, E. A., and Fliegelman, M. T.: Essential Familial Hypercholesterolemia, Ann. Int. Med. **29**:671, 1948.

Hemochromatosis, liver disease, or common duct obstruction may have hypercholesteremia without a rise in the neutral fats of the serum and hence have a clear serum. This type of hypercholesteremic xanthomatosis, secondary to liver disease, must be excluded by clinical findings and laboratory studies.

A high serum cholesterol excludes a normocholesteremic xanthomatous eruption. Inflammatory reaction or neoplasm as an etiological agent for xanthomatous lesions can be excluded by the history, physical examination, and biopsy.

There are numerous causes for the secondary eruptive xanthomatous lesions due to hypercholesteremia and hyperlipemia. Those listed are diabetes mellitus, chronic pancreatitis, lipid nephrosis, primary essential familial hyperlipemia and von Gierke's disease.[3] The xanthomatous lesions associated with myxedema in the previously reported cases have been assumed to be secondary eruptive xanthoma. We agree with this hypothesis.

PATHOGENESIS

The role of thyroid in the metabolism of lipids and cholesterol is not definitely known. Fat and sterols are absorbed and utilized in both hypothyroid and hyperthyroid states.[5] However, there is clinical and laboratory evidence that the thyroid hormone has some effect on the nitrogen-free phosphorus-containing compounds (cholesterol and fatty acids in combination to form esters). There is evidence that the thyroid hormone may effect nitrogen and phosphorus compounds of the lipid constituents of the blood[6] (lecithin and cephalin). In general, an increase in the serum cholesterol ester and lipid phosphorus is marked in a hypothyroid state. In hyperthyroidism the decrease of the serum cholesterol and lipid phosphorous is not pronounced.[6] Rarely myxedema may present a normal blood serum cholesterol, especially in the presence of hepatic disease of malnutrition.[7]

The thyroid hormone may have an indirect effect on the transportation of lipids within the blood plasma or possibly a direct effect on the endogenous synthesis of cholesterol and cholesterol esters.[6] Some authors believe that the point of attack of the thyroid hormones is on the phospholipids. They found a decrease of the phospholipids out of proportion to the decrease of serum cholesterol and cholesterol esters in hyperthyroidism.[6] Jackson and co-workers found that if there is a disturbance of the ratio of one moll of phospholipids to one moll of free cholesterol precipitation of cholesterol and cholesterol esters (milky serum) occurs.[8] Peters and Man demonstrated that only the phospholipids and cholesterol were affected in hypothyroidism or hyperthyroidism. Neutral fat was not affected in proportion to the serum cholesterol or phospholipids. These findings are borne out by the appearance of a clear serum in myxedema or hypothyroid states.[9] Ahren and Kunkel have shown that if the phospholipids in the plasma constitute 30% or more of the blood

5. Duncan, G.: Disease of Metabolism, Ed. 2, Philadelphia, W. B. Saunders Company, 1947, p. 869.

6. Means, J. H.: Thyroid and Its Diseases, Ed. 2, Philadelphia, J. B. Lippincott Company, 1948, p. 215.

7. Duncan.[5] Means.[6]

8. Jackson, R. S.; Wilkinson, C. F., Jr.; Hand, E. A.; Waldron, A. M., and Vogel, W. C.: The Relationship Between the Phospholipids and the Cholesterols in Human Plasma, Circulation **2**:472, 1950.

9. Peters, J. P., and Man, E. B.: Interrelations of Serum Lipids in Patients with Thyroid Disease, J. Clin. Invest. **22**:715, 1943.

lipids the plasma is clear. On the other hand, if the amount of the phospholipids is below 30% of the total blood lipids, the serum will be cloudy or lipemic. These factors are present regardless of a high or low level of the blood lipids.[10]

COMMENT

In view of the findings of Peter and Man, Thannhauser [11] assumes that myxedematous features aggravate but do not cause the disturbance of the fat transportation or deposition that leads to xanthomatosis. In regard to the three previously reported cases of myxedema and associated xanthoma, he states that they resulted from an idiopathic hyperlipermia which was further complicated by hypothyroidism. To prove this theory, studies of the neutral fats of the serum as well as the effect of a low-fat diet without thyroid medication must be observed in a similar case.

SUMMARY AND CONCLUSIONS

A case of hypercholesteremia, myxedema, and secondary eruptive xanthomatosis is reported which compares clinically with the three previously reported cases. Xanthomatous lesions, clinical myxedema, a low basal metabolic rate, high blood cholesterol and high cholesterol ester values are apparently characteristic of this entity. Involution of the xanthomatous lesions and improvement in the myxedema occurred during thyroid medication.

The hypothesis that myxedema with associated xanthomatosis is in reality xanthomatosis due to idiopathic hyperlipemia aggravated by myxedema could not be ruled out, but we do not believe that is the cause. Further studies pertaining to myxedema and associated xanthoma should be done with particular reference to the neutral fats, phospholipid-cholesterol ratio, and response to a low-fat diet without thyroid medication. By these determinations, the classification of "myxedema and associated xanthoma" as a secondary eruptive xanthoma would be more definite.

A study of the pedigree of this family through three generations excluded primary familial essential xanthomatosis of the hypercholesteremic type as a factor in the production of the xanthomas.

10. Ahrens, E. H., Jr., and Kunkel, H. G.: Stabilization of Serum Lipid Emulsions by Serum Phospholipids, J. Exper. Med. **90**:409, 1949.

11. Thannhauser, S. J.: Lipidoses: Diseases of Cellular Lipid Metabolism, Ed. 2, London, Oxford University Press, 1950, p. 224.

PILONIDAL SINUS OF THE HAND

MORRIS WAISMAN, M.D.
TAMPA, FLA.
AND
RENZO G. OLIVETTI, M.D.
ST. PETERSBURG, FLA.

AMONG barbers, penetration of cut hairs into the skin of the hand is a familiar occurrence. In 1946 and 1948, Patey and Scarff [1] described inflammatory and foreign body granulomatous reactions produced in the skin by buried hairs. Previously, in 1941, Allington and Templeton [2] had presented a similar case before the San Francisco Dermatological Society. Presumably the condition is more prevalent than the few reported cases would indicate, because to many of the victims such a relatively trivial and nondisabling occupational event hardly merits seeking medical consultation.

Clinically, there develops a pit or sinus between the fingers, from which protrude short, loose, easily removable hairs of different length, color, and texture. This sinus may become converted into an abscess, intermittently flaring up and discharging. Or the sinus may communicate a short distance proximally on the interdigital web with a nodule in which inflammatory manifestations are provoked by the embedded hairs. Because extraneous hairs cause the lesion and are constantly present, the term "pilonidal" is appropriately applied, indeed with even greater justification than in the case of the better-known sacrococcygeal sinus, which bears the same name.

Surveying the recorded cases of interdigital pilonidal sinus, we learn that lesions appear on the two hands with equal frequency. As a rule, only one interdigital space is affected, but in the case of Allington and Templeton [2] lesions evolved simultaneously in two interdigital spaces. Although any space may be affected, most of the reported lesions occurred between the third and fourth fingers. Perhaps the slightly forward position of the third interdigital web with relation to the rest of the hand explains its vulnerability to this kind of injury and accounts for the commonest localization of the interdigital sinus.

REPORT OF A CASE

A white man, 49 years of age, a barber, consulted us in November, 1951 because of a persistent lesion on his left hand. About three months previously he became aware of itching on the web between the left third and fourth fingers. Shortly afterward, he perceived and was able to extract a matted wad of hairs projecting from a tiny opening in the skin. One week later, a painless red nodule appeared a short distance away on the dorsum of the interdigital web. During the six weeks prior to his initial visit, the nodule had opened from time to time, discharging a small quantity of purulent secretion. At no time had there been any drainage from the original opening between the fingers.

1. Patey, D. H., and Scarff, R. W.: Pathology of Postanal Pilonidal Sinus: Its Bearing on Treatment, Lancet **2**:484-486 (Oct. 5) 1946; Pilonidal Sinus in a Barber's Hand: With Observations on Postanal Pilonidal Sinus, ibid. **2**:13-14 (July 3) 1948.

2. Allington, H. V., and Templeton, H. J.: A Case for Diagnosis (Foreign Body Reaction?), Arch. Dermat. & Syph. **45**:614-615 (March) 1942. Templeton, H. J.: Foreign Body Granuloma or Interdigital Cysts with Hair Formation, ibid. **46**:157-158 (July) 1942.

Fig. 1.—Interdigital pilonidal sinus and granuloma of web of hand. Wire probe has been introduced into sinus to demonstrate its continuity with granuloma.

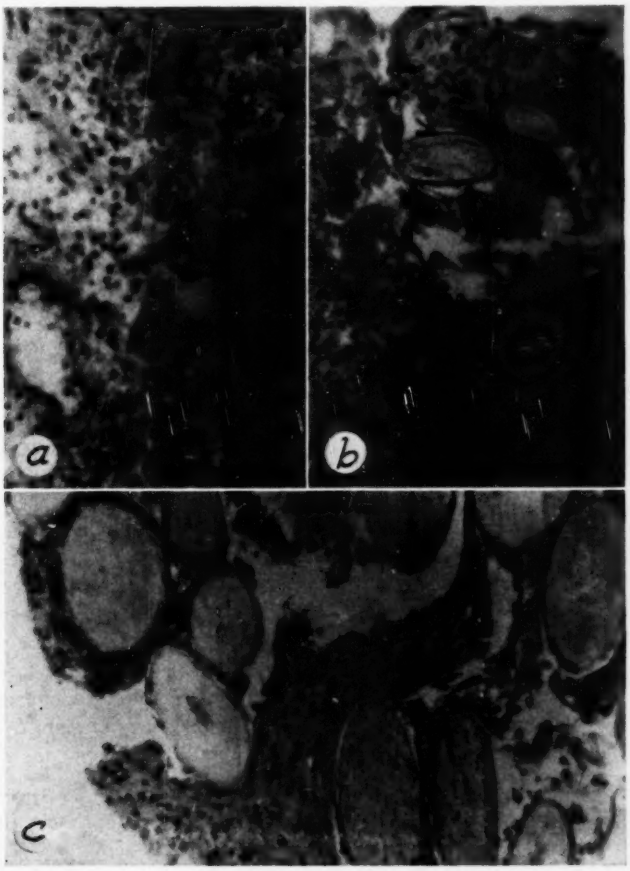

Fig. 2.—Pilonidal granuloma of hand. (*a*) typical foreign body granulomatous reaction with foreign body giant cells; (*b*) hairs embedded in granuloma; (*c*) mass of hairs extracted from center of granuloma, showing variation in diameter, color, and degree of disintegration of cuticular surface. × 440.

On examination a tiny puckered orifice was discerned on the web between the left third and fourth fingers. There was no evidence of inflammation in the skin surrounding it. On the web about 1 cm. proximally projected a moist, bright red vascular nodule measuring 5 mm. in diameter, with a nonindurated, slightly everted border which secreted a thin purulent fluid. The appearance was that of a pyogenic granuloma. A sterile, fine wire, introduced with ease through the distal opening, demonstrated a track which communicated with the granuloma (Fig. 1).

After the area was infiltrated with procaine, the track was incised down to the wire probe and laid open. Light curettage of the granuloma yielded fragments of red gelatinous tissue containing a few short hairs. The everted border of skin was trimmed. When the wire was then lifted from the wound, a mass of wadded hairs embedded in granulation tissue was discovered impaled upon its end.

The wound thus laid open was packed with a strip of petrolatum gauze. Healing proceeded rapidly; in a week the area had completely epithelized. A smooth inconspicuous scar resulted.

Microscopic examination (Fig. 2) disclosed a granulation tissue composed of fibroblasts, newly formed capillaries, lymphocytes, plasma cells, and rare focal collections of polymorphonuclear leucocytes. Occasional multinucleated giant cells of foreign body type were observed. Isolated hair shafts were embedded in the granuloma, but hair follicles were absent. The bundle of hair extracted en masse from the lesion showed hair shafts of varying diameters loosely surrounded by granulation tissue. A few hairs showed a central medulla; some contained considerable pigment in the cortex, and others exhibited no pigment at all. The cuticular surface on some hairs was adherent; on others, exfoliating or absent. The heterogeneous appearance indicated that the hairs were probably of diverse origin and had been lodged in the sinus for variable lengths of time.

COMMENT

The commonest instance of penetration of hairs into the skin occurs on beards, predominantly of Negroes, in the form of ingrown hairs.[3] The foreign body granulomatous reaction thereby produced, and the presence of an epithelial cuff around the "loop" hairs derived from follicular epithelium or epidermis, provide a close parallel with conditions prevailing in the interdigital pilonidal sinus.

Hairs which accumulate between a barber's fingers at his work may find their way into a minute depression of the skin, such as a crease, groove, or abrasion. A tiny pit is thereby produced. As more hairs are trapped, and especially with complicating infection, the opening persists and enlarges, and the track progressively elongates through the loose connective tissue of the interdigital web.

The ostium through which hairs enter may or may not be grossly visible. In some cases a small abscess in the web is the only manifestation of the lodgment of the hairs. In other cases hairs protruding from the opening indicate the persistence of the sinus, which can be intermittently the site of a scanty discharge. The opening may be tiny, adequate only to admit the finest bristle; but one barber related to us the case of a fellow-worker in which the sinus opening was ample to accommodate easily the tip of a lead pencil.

Histologically the lesion reproduces the features which characterize a nonspecific inflammatory granuloma. The irritative agent is represented by the foreign body, hair, with superimposed infection playing a concomitant role. Ewing[4] described a foreign body granuloma like that in our case, with collections of giant cells. In the cases of Allington and Templeton,[2] Patey and Scarff,[1] and King[5] the sinus track

3. Greenbaum, S. S.: Folliculitis Barbae Traumatica, Arch. Dermat. & Syph. **32**:237-241 (Aug.) 1935. Pinkus, H.: Chronic Scarring Pseudofolliculitis of the Negro Beard, Arch. Dermat. & Syph. **47**:782-792 (June) 1943.

4. Ewing, M. R.: Hair-Bearing Sinus, Letter to the Editor, Lancet **2**:427 (March 29) 1947.

5. King, E. S. J.: The Interdigital Pilonidal Sinus, Australian & New Zealand J. Surg. **19**:29-33 (Aug.) 1949.

was lined with squamous epithelium. In others granulation tissue lines the track. Sometimes the track becomes converted *in toto* into an abscess, whereas at other times it leads to an abscess or granuloma, as it did in this case, at some distance away. The structural variation among the hairs, and their disparate stages of cuticular disintegration, connote their accession into the sinus at different times.

Various theories have been advanced to explain how hair clippings perforate and become lodged in the skin. Tait [6] indicated that short hairs penetrate when the barber runs his fingers through the hair which he supports while cutting. Sames [7] believed that short bristly hairs were thrust and tamped into the soft skin of the web by the action of the comb which the barber holds while using the scissors with his other hand. Or, as an alternate possibility, he suggested that pressure resulting from the way the barber palms his scissors, using thumb and ring finger, might force hairs into the skin. Sames [7] further stated that he had frequently seen paronychia with foreign hair in lodgment, added evidence of the capacity of hair to penetrate the skin and cause infection. We have been informed by barbers that embedded foreign hairs in the skin of the forearms and abdomen are sometimes encountered. Ewing's patient thought that hair fragments penetrated into his hand while shampooing. Patey and Scarff [1] hypothesized that suction produced by the alternate tautening and loosening of tissues during movements of the fingers is sufficient to pull in hairs and thereby produce a sinus. Whatever mechanism is responsible for the penetration of hair, the sequence of events which leads to formation of a foreign body granuloma is well established.

Treatment of the pilonidal sinus usually requires surgical eradication, although some patients manage to keep free from recurrent trouble by the simple expedient of applying a strip of adhesive tape over the sinus opening, thereby preventing the access of new hairs.[5] Should acute infection, such as cellulitis or lymphangitis, be superimposed, fomentations and antibiotics are first employed. For removal of the sinus, excision and primary closure are suitable. Or, as in our case, it will suffice to incise and curette the lesion and allow the wound to granulate and heal over.

SUMMARY

A case of an interdigital sinus and hair-containing granuloma on the hand of a barber is presented. The lesion, produced by the occupational penetration of extraneous hairs into the skin, is literally "pilonidal," made up of the embedded hairs and the product of reaction of the surrounding tissue. Clinical features of the disease are reviewed, as are also observations regarding its pathogenesis. Lesions are usually single, affecting any interdigital space on either hand. Pathologically a sinus and/or an abscess or a foreign-body granuloma or combinations of these reactions are produced about the heterogeneous hairs. Treatment consists of either total excision or incision and curettage of the diseased tissue.

NOTE.—Since this paper was submitted for publication, an additional case of pilonidal sinus of the hand has been reported by Downing.[8]

1201 Citizens Building (2) (Dr. Waisman).

6. Tait, G. B.: Pilonidal Sinus in a Barber's Hand, Letter to the Editor, Lancet **2**:121 (July 17) 1948.

7. Sames, C. P.: Pilonidal Sinus in a Barber's Hand, Letter to the Editor, Lancet **2**:121 (July 17) 1948.

8. Downing, J. G.: Barbers' Pilonidal Sinus, J. A. M. A. **148**:1501 (April 26) 1952.

FURTHER STUDIES OF THE MOSAIC FUNGUS

E. SILVER DOWDING, Ph.D.*
EDMONTON, ALTA., CANADA

IN CLEARED preparations of skin taken from mycotic lesions, one often finds patches of refractile debris arranged in a network. This is the much-discussed "mosaic fungus." It is illustrated in a scale from a mycotic lesion on the palm of the hand (Fig. *2A*).

The filaments of the mosaic fungus may be from 4.5 to 12 μ in width. In small mosaic deposits, the central filaments are the widest while the peripheral ones are narrow and attenuated. The network is composed of linearly arranged segments, sometimes short and rectangular, sometimes long and sinuous.

Some believe that the mosaic fungus is the result of fungus infection; others, that it has no connection with mycosis. A number of years ago, Dowding and Orr summarized conflicting views about it in the Archives.[1] The present article is an account of observations carried out since that time.

ITS NATURE—FIVE INTERPRETATIONS

1. *Cholesterol.*—When the mosaic-fungus segments are viewed under polarized light and the microscope stage revolved, they alternately shine and are blacked out, i. e., they are birefringent. Because of this behavior, Davidson and Gregory conclude that they are cholesterol crystals,[2] a view widely held today. It has been known for a long time that cholesterol is a product of epidermal cornification.[3]

It must be remembered, however, that many substances besides cholesterol are birefringent under polarized light. Some of these are not even crystalline. I have found, for example, that the protoplasm of the dermatophyte Trichophyton mentagrophytes (Robin) Blanchard, growing under certain conditions, behaves in this way.

When the mosaic fungus is submitted to Schultz's modification of the Liebermann-Burchart acetic anhydride-sulfuric acid test,[4] a faint greenish color is sometimes

*Mrs. E. S. Keeping.

From the Provincial Laboratory of Public Health, University of Alberta. This investigation was made possible by financial assistance from the Dominion of Canada Department of Health.

1. Dowding, E. S., and Orr, H.: Transformation of Trichophyton Gypseum into Mosaic Fungus, Arch. Dermat. & Syph. **33**:865, 1936.

2. Davidson, A. M., and Gregory, P. H.: So-Called Mosaic Fungus as Intercellular Deposit of Cholesterol Crystals, J. A. M. A. **105**:1262, 1935.

3. Ruskind, R. R.: The Chemistry of Human Sebaceous Gland, J. Invest. Dermat. **17**:37, 1951.

4. Lillie, R. D.: Histopathologic Technique, Philadelphia, The Blakiston Company, 1948, p. 163.

observed before the segments dissolve in the acid. This has been interpreted as a positive test for cholesterol.[5] In our hands, the reaction is much too variable and the resulting color much too faint to be diagnostic.

Moreover, a simple test, now to be described, has convinced me that the mosaic fungus is not cholesterol. Skin containing mosaic fungus is mounted in 8% potassium hydroxide on a slide, sealed, and left undisturbed. At the same time (as a control), chemically pure cholesterol is mounted similarly. Within an hour or two, the large crystals of cholesterol are completely dissolved. On the other slide the much smaller segments making up the mosaic fungus, even after several months, are clearly visible, lacking the solubility of cholesterol.

2. *A Living Organism.*—There is little evidence to support the hypothesis that the mosaic fungus is a living organism. It is true that Weidman, to whom we owe the name "mosaic fungus," describes it as fungous[6] but in the adjectival sense meaning "resembling or originating from" a fungus.

Examination of Figure 2*A* reveals that the filaments of the mosaic fungus lack a cell wall. In this laboratory, the periodic acid (Schiff) stain for fungous cell-wall substances[7] used on the mosaic produces no red color. Unlike true mycelium, the mosaic fungus dissolves in xylene without leaving a trace of cell membrane. Since it lacks a cell wall, it cannot be a living dermatophyte. Furthermore, no one has ever succeeded in cultivating it on an artificial medium. In short, findings from this laboratory support the general opinion that the mosaic fungus is dead material.

3. *An Artifact.*—Bruhns and Alexander[8] have suggested, though without definite evidence, that the mosaic fungus is produced by the potassium hydroxide mounting medium.

I have found that the mosaic is visible in tissues cleared in lactic acid instead of potassium hydroxide. Furthermore, MacKee and Lewis have distinguished it in xylene mounts.[9] It is scarcely credible that these different chemical substances should produce identical-appearing artifacts.

Most writers however, including editors of standard medical dictionaries,[10] define the mosaic fungus as an artifact. "Artifact" could be defined as "a substance that is not a natural product." This meaning applied to the mosaic fungus implies that it owes its origin to the chemical substance in which the skin is mounted rather than to living cells. I am convinced that the mosaic fungus should not be described in this sense as an artifact.

4. *A Product of Epidermal Cells.*—It is true that the mosaic fungus network conforms in its size and shape to the epidermal cells of the skin. However, if it is a

5. Cornbleet, T.; Schorr, H. C., and Popper, H.: The Mosaic Fungus: A Cholesterol Intercellular Artifact, Arch. Dermat. & Syph. **48**:282, 1934.

6. Weidman, F.: Laboratory Aspects of Epidermophytosis, Arch. Dermat. & Syph. **15**:415, 1927.

7. Klingman, A. M., and Mescon, H.: The Periodic Acid-Schiff Stain for the Demonstration of Fungi in Animal Tissue, J. Bact. **60**:415, 1950.

8. Bruhns, C., and Alexander, A. I., in Jadassohn, I.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Springer-Verlag, 1928, Vol. 11, pp. 89 and 464.

9. MacKee, G. M., and Lewis, G. M.: Keratolysis Exfoliation and the Mosaic Fungus, Arch. Dermat. & Syph. **23**:445, 1931.

10. (*a*) Blakiston's New Gould Medical Dictionary, Philadelphia, The Blakiston Company, 1949. (*b*) Dorland, W. A. N.: The American Illustrated Medical Dictionary, Ed. 22, Philadelphia, W. B. Saunders Company, 1951.

product of the epidermal cells of the host, one would expect to find it sometimes in skin that has not been parasitized by a fungus. Such a discovery has not been recorded. MacKee and Lewis [9] systematically searched for the mosaic fungus in such nonmycotic lesions as psoriasis, lichen planus, pityriasis rosea, pemphigus, sunburn, and seborrhea, without success. Therefore, if it is an excretion of the epidermal cells, it must be a specific response to a dermatophyte.

If the mosaic fungus were excreted by the host cells it would be expected to occur in three-dimensional sheets bent round to conform to the curvature of the cell. Instead of this, the components of the mosaic fungus are linear, looking more like a cast of hyphae than of spherical cells. It does not seem probable to me that the mosaic fungus is a product of epidermal cells.

5. *A Fungous Product.*—There remains the hypothesis, previously suggested,[1] that the mosaic fungus is a fungous product.

One collection of toe-nail scrapings which contained a quantity of mosaic fungus showed abundant hyphae and spores of Aspergillus sydowii. This tissue consistently yielded uncontaminated cultures of A. sydowii. With this exception, all the mosaic fungus observed in this Province was associated (as has been true in the past [1]) with the dermatophyte T. mentagrophytes.

Material was sent to this laboratory over a period of months from a patient with chronic epidermophytosis of the feet. It was found repeatedly that when the amount of T. mentagrophytes mycelium became less mosaic fungus appeared in the tissue.

It was also observed that when patients are recovering from Trichophyton skin infections the amount of mycelium in the lesions decreases while the mosaic fungus becomes more plentiful.

Sometimes epidermal scales contain both mycelium and mosaic fungus intimately associated. Figure 2 *B* shows such a relationship. Both the fungal hyphae and the mosaic segments contribute to the same network, and it can be seen that both are of the same shape and size and, indeed, are so similar that they are difficult to distinguish. Only the more shriveled appearance of the mosaic segments sets them apart from the hyphae.

These further observations support the earlier assumption [1] that the mosaic fungus is of fungous origin.

A THEORY OF THE FORMATION OF THE MOSAIC FUNGUS

Formation of the Mosaic Material.—The steps in the transformation from the dermatophyte hypha to the mosaic fungus were previously assumed [1] to be as follows: 1. Globules appear in the cytoplasm and enlarge to the diameter of the hypha. 2. The cell walls of the hypha become dissolved. 3. The globules are converted to the angular refracting segments of the mosaic fungus. More recent observations have corrected these assumptions.

It is well known that molds, as they grow into the air, excrete liquid drops through their hyphal walls. Buller [11] has observed that on certain species, as these drops dry, they become angular in shape, showing that they are composed not of pure water but of a solution of chemical substances. Experiments described below suggest that dermatophytes behave similarly.

11. Buller, A. H. R.: Researches on Fungi, Vol. 4, New York, Longmans, Green & Co., 1934, p. 87.

Six guinea pigs were inoculated upon the shaved abdomen with T. mentagrophytes by the method used by deLamater and Benham.[12] Eight to 10 days after inoculation, in the exfoliating scales from the lesions, mycelium was abundant. It was composed of hyphae and of chains of spores (oidia). Many of the hyphae and spore-chains possessed an external sheath made up of refractile material (Fig. 1 *A*). This material was usually to be found surrounding the faint cell walls of empty disorganizing hyphae as a double row of shiny deposits. On the eighth day after inoculation these deposits were so close to the hypha cell walls as to be indistinguishable from them, but a day or two later they became separated by a narrow space from the hyphae. The experiment was repeated with another six animals, and 10 days after inoculation the scales of three of these showed similar refractile deposits.

Among the specimens of fungus-infected tissue from human patients sent to this laboratory, one particular sample (from the cheek) was prolific in mycelium. Most of the hyphae were densely filled (except for small vacuoles) with finely granular protoplasm. Some complete hyphae and sections of others had died. These were empty of contents but their cell walls had persisted (Fig. 1 *B*). Close to the outer surface of many of them were angular refractile deposits (Fig. 1*B*).

It appears from the observations recorded above that a dermatophyte growing in epidermal tissue may produce extrahyphal deposits and that after the mycelium has become disorganized the dead hyphal cell walls and the extrahyphal deposits may remain visible in the tissue.

Individual segments of the mosaic fungus may be described briefly as follows: The segments at first glance are geometric. They have, in fact, been described as crystals with reentrant angles,[2] but the crystal-like regularity is not so evident upon detailed study. Under high magnifications the segments are markedly frayed, channeled, and pitted (Fig. 1 *D*). (Weidman has aptly called them "moth-eaten".[6]) Careful examination shows that they may be joined to one another by connecting strands at their edges so that they form a ribbon. They do not always lie flat but may be rolled at the edges (Fig. 1 *D*). They frequently occur as a collection of rounded droplets (Fig. 2 *A*, lower center). Figure 1 *C* (tissue from foot lesions) shows mycelium and mosaic fungus in close association. Mosaic segments can be seen to overlie, or lie closely alongside, a hypha. They appear as a double row on either side of the spores. In their distribution and in their morphology they resemble extrahyphal deposits.

In photographs of mosaic fungus taken in this laboratory, faint traces of fungus cell walls were sometimes distinguished. For example, in a piece of tissue from the foot mosaic fungus was very obvious but no mycelium could be found until a photograph of it (Fig. 3 *A*) was examined. Then a careful examination of the central area (lying between portions of mosaic network) revealed faint parallel lines running straight through the tissue. Photographs of the mosaic fungus published by other workers were then scrutinized, and in some of them [5] similar lines were observed. They must surely be interpreted as being persistent cell walls of the disorganized mycelium from which the mosaic fungus was originally excreted.

Formation of the Mosaic Pattern.—When a hypha grows in the skin, it makes an easily distinguished channel through it. Filaments of mosaic fungus are sometimes

12. deLamater, E. D., and Benham, R. W.: Experimental Studies with Dermatophytes 1, J. Invest. Dermat. **6**:451, 1938.

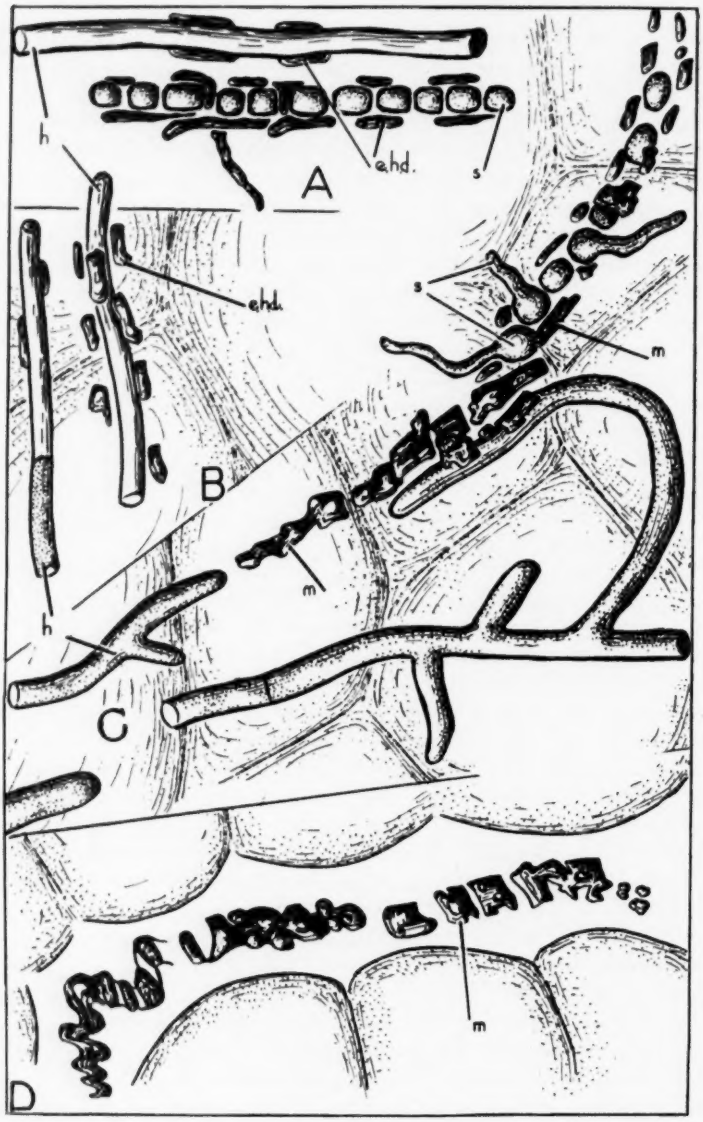

Fig. 1.—Trichophyton mentagrophytes, extrahyphal deposits, and mosaic fungus in the skin: *A*, hypha and spores in epidermis of guinea pig; *B*, disorganizing hyphae in epidermis of human cheek; *C*, hyphae and germinating spores in epidermal tissue from foot, together with mosaic fungus segments; *D*, tissue similar to *C*, with mosaic fungus only. *h*, hypha; *s*, spore; *e. h. d.*, extra hyphal deposit; *m*, mosaic fungus. × 1,000.

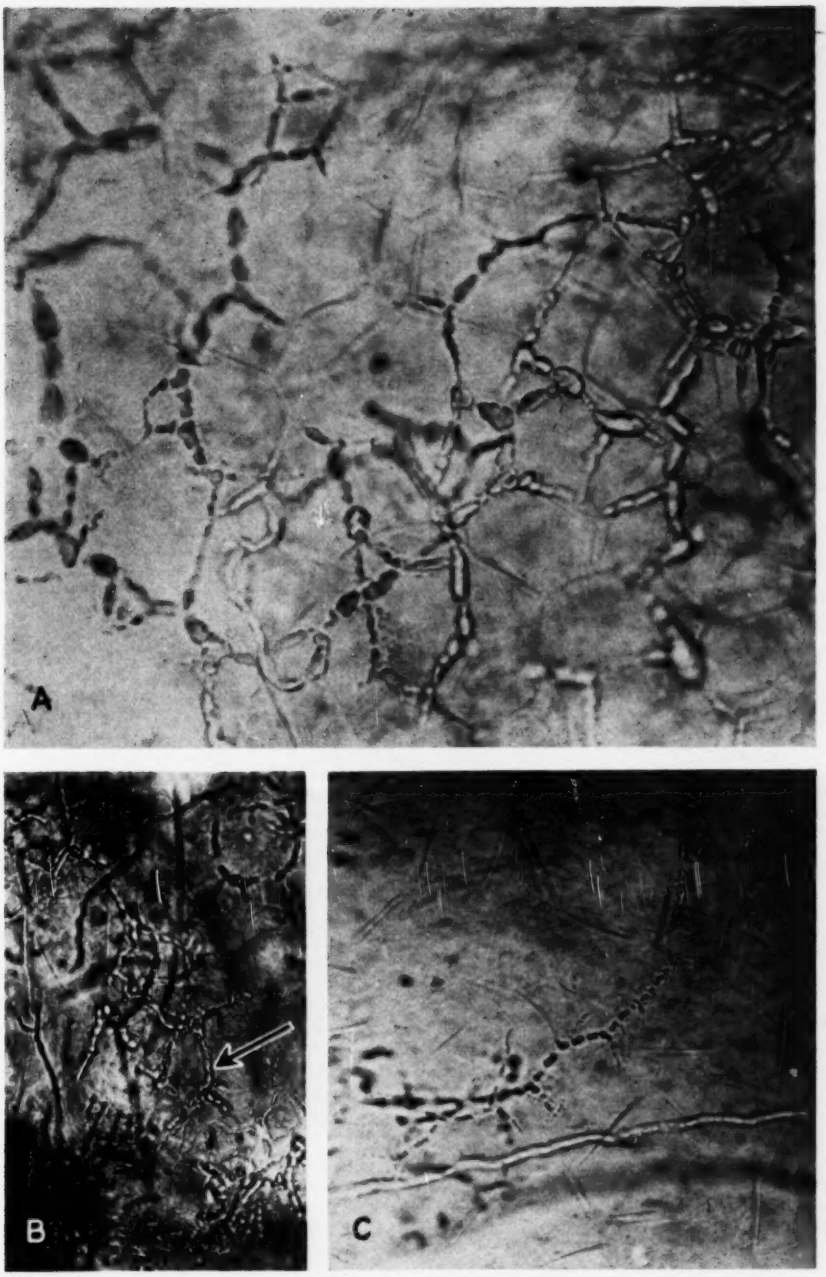

Fig. 2.—*A*, mosaic fungus in skin from palm; *B* and *C*, in skin from foot. *B* shows a network (center of photograph) made up of hyphae at left, and mosaic fungus (arrow) at right.

C, mosaic fungus which may have been derived from the hypha below it. *A*, × 1,000; *B*, × 325; *C*, × 500.

Fig. 3.—*A*, mosaic fungus in tissue from foot, showing faint cell walls of disorganized hyphae in center.

B, photograph of part of tissue drawn in Figure 1 *C*, showing at lower left very faint mosaic segments (arrow) overlying the hypha *A*, × 750; *B*, × 1,000.

found in the skin channel in which they were originally deposited by the hypha (Fig. 1 *D*). Often, however, they are not found in these channels. It would seem that they have changed their position. In fact, such a movement has been observed. When wet preparations showing mosaic fungus and mycelium in close proximity are being watched under the microscope, if the cover slip is inadvertently moved the mosaic segments can be seen to scatter some distance away from the hyphae.

An observation not previously recorded, but having bearing on the formation of the mosaic pattern, is this: When mosaic fungus and mycelium are both present in the skin, the mosaic is usually found at a slightly higher level, i. e., nearer the cover slip. In the clearing medium it becomes visible a few minutes later than does the mycelium.

In the light of this observation, Figure 3 *A* may be interpreted as follows: The hyphal excretions have drifted from the original position along the hyphae and become deposited, while they were in the mounting fluid, at a slightly higher level, taking the form of a network in conformity with the epidermal cells below it.

Again, in Figure 2 *C* it can be seen that the mosaic fungus extending diagonally across the photograph is of the same length as the hypha below it and may well be interpreted as an excretion of it. Peripheral strands of mosaic material seem to have been drawn out from the main filament into the intercellular spaces of epidermal cells.

It is therefore suggested that the material in the mosaic fungus originates from a dermatophyte, passes through the cell walls of the hypha, rises in the mounting medium through the epidermal cells of the skin, and collects into a mosaic pattern near the cover slips.

SUMMARY

1. Evidence has been given to show that the mosaic fungus is neither cholesterol, nor a living fungus, nor an artifact of the mounting medium, nor is it likely to be a product of the epidermal cells. The most probable explanation of its origin is that it is a fungous product.

2. Careful scrutiny of skin containing mosaic fungus sometimes reveals faint traces of the persistent cell walls of disorganized hyphae.

3. Hyphae and spores of the ringworm fungus Trichophyton mentagrophytes when growing in the skin may produce extracellular deposits which resemble the mosaic fungus.

4. I interpret the mosaic fungus as the extracellular deposit of a dermatophyte.

5. In potassium hydroxide preparations, the reticulate pattern of the mosaic fungus and its position on a focal plane superior to that of the cells of the epidermis may be explained as follows: Capillary forces carry up the mosaic segments toward the cover slip. As the segments drift upward, they pass around the epidermal cells and, in conforming to their shape, become arranged in a reticulate pattern.

CHRONIC ULCERS OF THE LEG ASSOCIATED WITH BLOOD DYSCRASIAS

FRANCES PASCHER, M.D.
AND
RALPH KEEN, M.D.
With the Technical Assistance of Florence Simm, B.A.
BROOKLYN

BLOOD dyscrasias, particularly the congenital hemolytic anemias,[1] are of primary importance in a consideration of the possible causes of chronic recurrent ulcers of the leg. An association of leg ulcers with sickle cell anemia is generally better appreciated than the relationship of this symptom to other forms of congenital hemolytic anemia, e. g., congenital hemolytic icterus (familial acholuric jaundice, spherocytic anemia) and Mediterranean disease (Cooley's anemia, thalassemia).

In a review of the subject of indolent ulcers of the leg in diseases of the blood, in addition to the conditions already mentioned, Gendel [2] lists the following: Banti's syndrome, thrombocytopenic purpura, Gaucher's disease, pernicious anemia, and chronic hemolytic polycythemia. The latter was presented before the Royal Society of Medicine by Rau, Pulvertaft and Humble.[3] Gendel [2] did not include polycythemia vera (erythremia, Osler-Vaquez disease). However, ulcerations of the lower extremities [4] and peripheral vascular complications have been reported by others in this dyscrasia.[5]

The incidence of leg ulcers in sickle cell anemia has been variously estimated at 25.7% [6] and at 75%.[7] The probable incidence of this symptom in congenital hemolytic icterus has been given as 6.5%.[2] No statement can be made as yet as to

From the Department of Dermatology and Syphilology, New York University Post-Graduate Medical School (Chairman, Dr. Marion B. Sulzberger), and the Skin and Cancer Unit of the University Hospital.

1. (*a*) Vilanova, X.; Piñol Aguadé, J., and de Dulanto, F.: Skin Manifestations of Hemolytic Jaundice, Actas dermo-sif. **40**:608-624, 1949. (*b*) Cummer, C. L., and La Rocco, C. G.: Ulcers of Legs in Sickle Cell Anemia, Arch. Dermat. & Syph. **42**:1015-1039, 1940.

2. Gendel, B. R.: Chronic Leg Ulcer in Diseases of the Blood, Blood **3**:1283-1289, 1948.

3. Rau, L.; Pulvertaft, R. J. V., and Humble, J. G.: Chronic Hemolytic Polycythemia, Proc. Roy. Soc. Med. **39**:307-308, 1946.

4. Hallam, R.: Ulcerated Nodules on the Legs Associated with Splenomegalic Polycythemia, Brit. J. Dermat. **42**:292-293, 1930.

5. (*a*) Norman, I. L., and Allen, E. V.: Vascular Complications of Polycythemia, Am. Heart J. **13**:257-274, 1937. (*b*) Zeiter, W. J.: Peripheral Vascular Disturbances in Polycythemia, M. Clin. North America **24**:485-492, 1940.

6. McGavack, T. H., and Nussbaum, C. C.: Skin Manifestations of Sickle Cell Anemia, Urol. & Cutan. Rev. **46**:194-199, 1942.

7. Gendel.[2] Diggs, L. W., and Ching, R. E.: Pathology of Sickle Cell Anemia, South. M. J. **27**:839-845, 1934.

the frequency of the association of ulceration of the leg with Mediterranean disease. The only publication to our knowledge on the occurrence of leg ulcers in this form of anemia is that of Estes, Farber, and Stickney.[8] Dameshek [9] likewise has observed a case of chronic leg ulcer in this blood dyscrasia.

The purpose of this report is to bring to the attention of the dermatologists the importance of the blood dyscrasias in the pathogenesis of chronic ulcers of the lower extremities by describing a group of unusual cases. The group includes a case of sickle cell anemia [10] in which leg ulcers appear later in life than in most cases hitherto reported; a case of familial hemolytic jaundice associated with arteriosclerosis obliterans in which one of the ulcers ultimately gave rise to a prickle cell epithelioma; a case of Mediterranean disease [11] with recurrent ulcers of the legs; a case of polycythemia symptomatica associated with a leg ulcer, and a case of polycythemia vera associated with a leg ulcer and multiple ulcerations of the skin.

REPORT OF CASES

CASE 1.—A. R., a Negro woman, aged 38, presented herself at the Skin and Cancer Unit of University Hospital on July 25, 1945. The first ulcer appeared on the right leg when the patient was 34 years old.

Physical Examination—Examination disclosed pallor of the mucous membranes, an icteroid tint to the sclera, an enlarged heart, and an enlarged spleen, palpable 4 cm. below the costal margin. An elongated irregular scar with a small ulcer in the center was seen on the medial aspect of the right ankle. Scarring of a more superficial character was present on the medial aspect of the left ankle. Hyperpigmentation about the scars and some superficial varicosities were found on both legs. A detailed examination of the peripheral circulation, by consultants in this field, failed to disclose evidence of vascular disease. All concurred in the opinion that the varicosities were not clinically significant.

Investigations.—Repeated examinations during an observation period of five years showed some fluctuation in the degree of the anemia. The erythrocyte count varied between 1,700,000 and 2,500,000 cells per cubic millimeter and the hemoglobin concentration between 6.1 gm. per 100 cc. (42%) and 7.8 gm. (54%). Sickling of the red blood corpuscles, anisocytosis, achromia, and polychromasia were demonstrable at all times.

The icterus index was increased on three occasions: 13.0 units, 15.0 units, and 13.6 units (normal 4 to 6 units). Both the direct van den Bergh and the indirect van den Bergh tests were positive. A urobilin determination showed 70 mg. per 24 hours (normal 0 to 30 mg.). Serologic tests for syphilis gave negative reactions.

Histologic examination of the margin of the ulcer failed to reveal any specific change. The Perl reaction (potassium ferrocyanide stain for hemosiderin) was negative.

Diagnosis.—The diagnosis was sickle cell anemia with sickle cell ulcer.

CASE 2.—J. P., a white woman, aged 62, born in Hungary, was first seen at the Skin and Cancer Unit on Aug. 26, 1942. A history of a familial blood dyscrasia was not obtained. The patient stated that she had had recurrent ulcers of both legs for many years. Four years prior to admission a "growth" appeared on the lateral aspect of the right ankle. Histologic examination of the fungating mass was reported to have shown a squamous cell carcinoma (grade 1).[12]

8. Estes, J. E.; Farber, E. M., and Stickney, J. M.: Ulcers of the Leg in Mediterranean Disease, Blood **3**:302-306, 1948.

9. Personal communication to the authors.

10. Presented before the Bronx Dermatologic Society, Nov. 16, 1950.

11. Presented before the Bronx Dermatologic Society, Nov. 16, 1950, and referred to in an earlier report (Pascher, F.; Richter, M. N.; Bellach, H., and Simm, F.: Sternal Marrow Findings in Various Dermatoses, A. M. A. Arch. Dermat. & Syph. **66**:251-275, 1952).

12. This report was supplied by the Warren Hospital, of Phillipsburg, N. J.

Physical Examination.—Physical examination disclosed an icteroid pallor of the skin, sclera, and mucous membranes. The spleen was massive, extending beyond the midline and below the level of the umbilicus. The blood pressure reading was 150/80 mm. Hg.

Both legs appeared abnormally thin, owing to wasting of the muscles and the subcutaneous fat. The skin over the tibia and dorsa of the feet was shiny, smooth, thickened, cool to the touch, and adherent to the underlying fascia. Areas of hyperpigmentation and depigmentation were irregularly distributed over both legs. The peripheral pulses could not be felt. A fungating

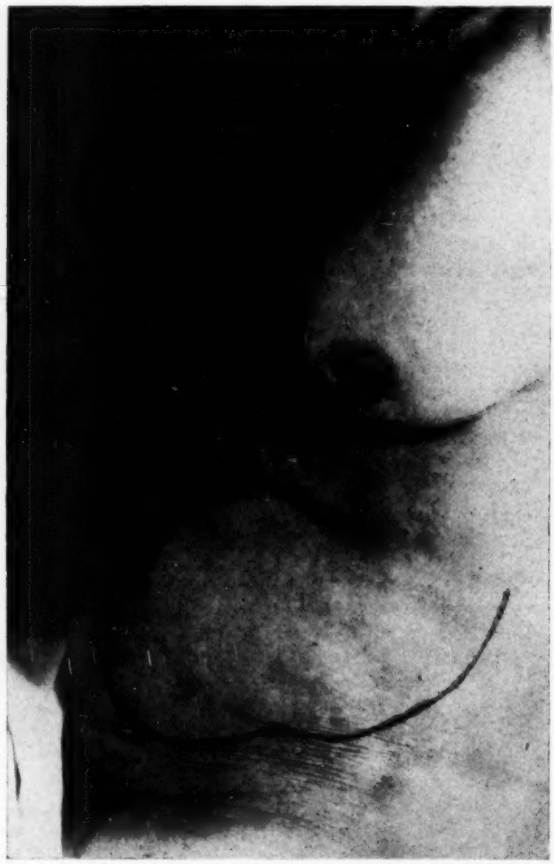

Fig. 1.—Massive splenomegaly in a case of congenital (?) hemolytic icterus with arteriosclerosis obliterans.

cauliflower-like mass measuring approximately 10 by 10 cm. covered the lateral aspect of the right heel and ankle. On the left leg, a shallow ulcer, 2.5 by 2.5 cm., was found above the malleolus.

Investigations.—A consistent alteration in the hemogram was found on four different occasions. The erythrocytes averaged 2,700,000 per cubic millimeter and the hemoglobin 6.9 gm. per 100 cc. The reticulocyte count was 5.9% on one occasion and 31.1% on another. Qualitative studies disclosed moderate anisocytosis, microcytosis, an occasional normoblast, and moderate polychromasia. The mean corpuscular diameter measured 6.3μ (normal 7.0 to 8.0μ). A fragility test revealed that hemolysis started at 0.675% (control, 0.495%) and was completed at 0.315%

(control, 0.34%). Repeated tests for sickling gave negative results. The icterus index measured 21.4 units (normal 4 to 6 units), the direct as well as the indirect van den Bergh determinations gave positive reactions, and the serum bilirubin measured 2.2 mg. per 100 cc. (normal, less than 1.0 mg. per 100 cc.). The blood Wassermann reaction was negative. Repeated urinalyses gave negative reactions for sugar and albumin.

Histologic examination of the fungating mass on the right ankle again disclosed a squamous cell carcinoma (Grade 1). A roentgenogram showed atrophy of the bony and soft tissues of the legs and feet and calcification of the arteries. The soft tissues over the right lateral malleolus were also the seat of a nodular fibrous-like thickening and calcification.

Diagnosis.—The diagnoses were congenital (?) hemolytic icterus and arteriosclerosis obliterans associated with chronic recurrent ulcers of the legs and epitheliomatous alteration (squamous cell) of the ulcer of the right leg.

Fig. 2.—Ulcerations of both ankles and a fungating squamous cell carcinoma of the right ankle in a case of congenital (?) hemolytic icterus with arteriosclerosis obliterans.

CASE 3.—J. C., a white woman, aged 37, of Italian descent, consulted one of us (F. P.) on May 11, 1949, because of a recurrent ulcer of the right ankle. She was referred to the New York Skin and Cancer clinic for study.

History.—Two relatives, a sister and a niece, were examined and a hematologic picture of Mediterranean disease was found. The ulcer of the right leg, which appeared five years prior to admission, had healed and recurred several times. With each recurrence the lesion became less amenable to treatment. The patient also had had ulcers on the left leg which healed without difficulty. She was not aware of having anemia until 18 months prior to admission.

Physical Examination.—The essential findings were an icteroid pallor of the skin and sclera, an enlarged spleen extending to the umbilicus, and an ulcer above the right lateral malleolus. The ulcer measured 4 by 4 cm. and had a punched-out appearance and a sclerotic base devoid of granulation tissue. Surrounding the ulcer was an irregular, broad zone of purpura. The affected area was exquisitely tender. Several scars and patches of hyperpigmentation were distributed on both legs.

Investigations.—Repeated examinations of the peripheral blood showed a consistent alteration in the hemogram. The erythrocytes ranged between 2,500,000 and 2,900,000 cells per cubic millimeter; the hemoglobin varied between 6.8 gm. (45%) and 7.3 gm. per 100 cc. (53%), and the leucocytes numbered 8,000 to 10,000 cells per cubic millimeter. The differential count was within normal limits. Marked anisocytosis, moderate anisochromia, poikilocytosis, frequent target cells, occasional polychromatic cells, and normoblasts (1 to 4%) were among the qualitative changes

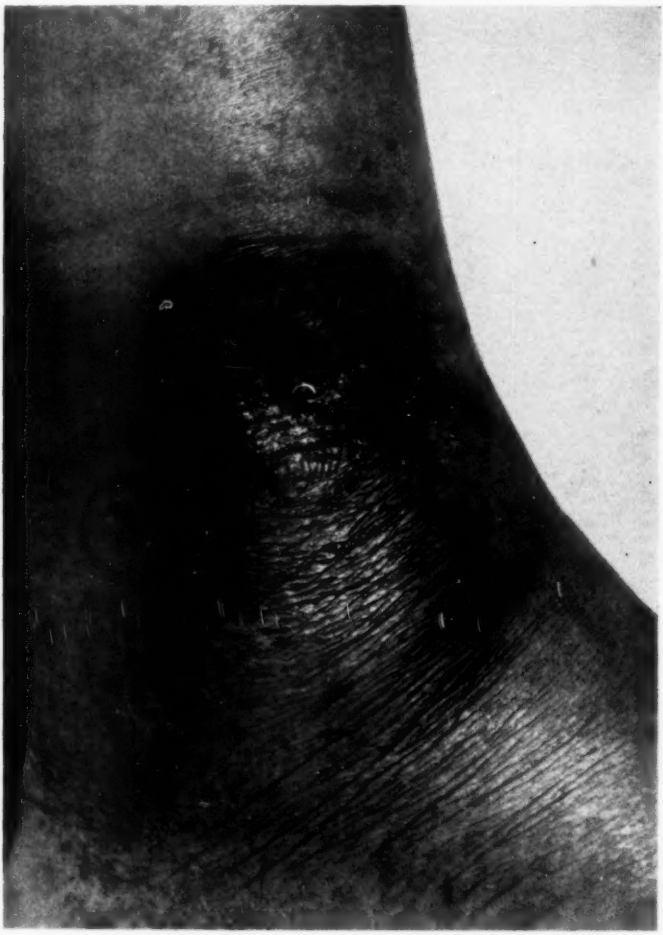

Fig. 3.—Indolent ulcer with an areola of purpura on the lateral aspect of the right ankle in a case of Mediterranean disease.

noted. The reticulocyte count was 1.8% on one occasion and 4.4% on another. The platelets were somewhat reduced in number on two determinations—176,000 and 150,000 per cubic millimeter respectively (normal, 200,000 to 350,000 per cubic millimeter) and within normal limits on two examinations. The bleeding time, clot retraction, and clot fragility tests disclosed no abnormalities on three successive examinations. A tourniquet test elicited no petechiae. Hemolysis of the red cells started at 0.43% (control, 0.44%) and was complete at 0.28% (control, 0.34%) in the first fragility test. In the second test hemolysis was initiated at 0.32% (control, 0.44%) and was

completed at 0.20% (control, 0.34%). Repeated examinations for sickling gave negative results. Sternal aspiration and examination of the marrow disclosed an erythroblastic hyperplasia and hemosiderosis of the marrow.[13]

The icterus index measured 25.0 units (normal 4 to 6 units) and both the direct and the indirect van den Bergh tests gave positive reactions. A serum bilirubin assay showed a trace (normal 0.5 to 1 mg. per 100 cc.). The urobilin output was 44 mg. per 24 hours (normal, 0 to 30 mg.). The Coombs test[14] and serologic tests for syphilis gave negative reactions.

Histologic examination of the margin of the ulcer revealed no noteworthy change except for a diffuse cellular reaction consisting of small round, wandering connective tissue cells, fibroblasts, and chromatophores laden with pigment. The pigment granules were deposited extracellularly as well as within the chromatophores. The potassium ferrocyanide stain elicited a striking reaction (Perl).

Course.—The patient was given two transfusions of 500 cc. of whole blood. A transitory improvement in the blood picture followed, but there was no apparent change in the ulcer. The lesion healed after two months of topical treatment and local supportive measures. Recurrences followed.

Diagnosis.—The diagnosis was Mediterranean disease (Cooley's anemia) associated with chronic recurrent ulcers of the legs.

CASE 4.—I. L., a white woman, aged 55, consulted one of us (F. P.) on July 9, 1945, because of an eruption that had appeared approximately six weeks previously.

History.—The diagnosis of polycythemia vera had been established a number of years previously. In March, 1945, she was hospitalized because of ataxia, motor aphasia, and diplopia. A few months later a painful ulcer, which proved resistant to treatment, appeared near the right ankle. Within two weeks several tender crusted lesions appeared on other parts of the body.

Physical Examination.—The patient appeared chronically ill and exhibited a distinct cyanosis of the lips, tongue, and mucous membranes. She found walking difficult, and her speech was hesitant and blurred. A gyrate, violaceous, indurated, and crusted plaque with satellite lesions was found on the left breast and a silver-dollar-sized, button-shaped granulomatous lesion was seen on the anterior aspect of the left thigh. The right foot was violaceous and swollen. Proximal to the ankle were two punched-out superficial ulcers.

Reexamination a month later disclosed that the lesion on the left thigh had ulcerated and that the lesions on the left breast had increased in diameter. New areas were involved. A malodorous granulomatous mass with a necrotic center and an erythematous halo was present on the left leg, and a few pustules were distributed over the lower extremities.

The patient was admitted to Montefiore Hospital[15] on Sept. 27, 1945. Neurological examination disclosed a coarse tremor and exaggerated reflexes on the right, sustained right ankle clonus, deviation of the tongue to the left, and bilateral ptosis of the palate. The initial blood pressure was 128/88 mm. Hg. Subsequent readings showed a gradual rise to 180/100 mm. Hg. The liver was palpable 1 fingerbreadth below the costal border. The spleen, however, could not be felt. Oscillometric readings showed that the peripheral arteries were patent and that there were no evident signs of intravenous thrombosis.

Investigations.—Histologic examination of a lesion on the breast revealed changes similar to those observed in erythema multiforme, except for the somewhat more pronounced vascular changes. Bacteriologic examination of one of the large pustules resulted in a sterile culture.

The initial hemogram showed 15 gm. of hemoglobin, 5,080,000 erythrocytes and 6,700 leucocyte cells per cubic millimeter. The differential count was within normal limits, as was the hematocrit reading of 41% (normal 40 to 45%). One month later, the hemoglobin rose to 17.5 gm. per 100 cc., the red blood corpuscles to 6,300,000 per cubic millimeter, and the hematocrit

13. Dr. Maurice N. Richter supplied this report.

14. A serological test to demonstrate the presence of isoantibodies and autoantibodies (Coombs, R. R. A.; Mourant, A. E., and Race, R. R.: A New Test for the Detection of Weak and Incomplete Rh Agglutinins, Lancet **2**:15-16, 1945).

15. The staff of Montefiore Hospital for Chronic Diseases supplied a summary of their findings.

reading to 51%, and the blood volume to 93 cu. mm. per kilogram (normal, 78 to 97 cu. mm. per kilogram). Chemical analysis of the blood, serologic tests for syphilis, and repeated urinalyses did not disclose any abnormalities.

Course.—Phlebotomies were performed at intervals; large doses of vitamins were administered orally, and 1% aqueous solution of brilliant green was applied daily to the cutaneous lesions. The patient responded satisfactorily to this regimen.

Fig. 4.—Ulcer of the midsection of the left leg in a case of polycythemia associated with pulmonary fibrosis and superficial thrombophlebitis.

Diagnosis.—The diagnosis was Gaisböck's syndrome (polycythemia vera with hypertension) associated with multiple cerebral thrombotic episodes and multiple ulcerations of the skin.

Case 5.—S. M., a white woman, aged 65, presented herself at the Skin and Cancer Clinic on Sept. 9, 1940, because of an ulcer of six months' duration on the left leg.

History.—A few months prior to admission, the patient had been informed that she had "too many red blood corpuscles." Swelling of the left leg preceded the development of the ulcer by two months.

Physical Examination.—The patient was moderately obese and plethoric. Her face, lips, tongue, mucous membranes, hands, legs, and feet were distinctly cyanotic. Approximately 10 to

12 bluish-red angiomata,[16] elevated 2 to 4 mm. above the surface of the skin, varying from 0.4 cm. to 1.0 cm. in diameter were distributed over the chest, breasts, abdomen, and back. The skin over the anterior aspect of the left leg was more intensely violaceous than the surrounding skin. In the center of this purpuric, edematous zone was a superficial quarter-sized ulceration. Some superficial varicosities were noted on both lower extremities. The splenic edge was palpable 3 fingerbreadths below the costal margin, and the blood pressure measured 170/80 mm. Hg.

Investigations.—Repeated blood counts showed that the erythrocyte count varied between 6,600,000 and 7,300,000 cells per cubic millimeter and the hemoglobin between 16.2 and 17.5 gm. per 100 cc. The leucocytes were within normal limits except for an increase in the band forms, which made up 12 to 15% of the differential count. The hematocrit reading was 63% (normal, 40 to 45%).

A roentgenogram disclosed changes in the lungs that were diagnosed as "chronic tuberculous-type peribronchial and miliary-like infiltration of both central lung fields."

Diagnosis.—The diagnosis was polycythemia associated with multiple angiomata, thrombophlebitis, ulceration of the left leg and pulmonary fibrosis secondary to chronic tuberculosis.

COMMENT

The diagnosis of hemolytic anemia in Cases 1, 2, and 3 was based on the reduction in the total number of erythrocytes and hemoglobin together with evidence of increased hemolysis of the red blood corpuscles. Determination of the particular type or form of hemolytic anemia depended on the demonstration of special features: sickling in Case 1; increased fragility of the erythrocytes in hypotonic solutions of sodium chloride in Case 2; a history of familial anemia, the patient's ancestry (Italian descent), and the decreased fragility of the erythrocytes as determined by the fragility test in Case 3.

The relatively mature age of the patient with sickle cell anemia (Case 1) when the leg ulcers first appeared is of some interest. In the majority of cases, this manifestation of the disease occurs between the ages of 10 and 25 years.[6] Isolated reports of persons over 30 years of age with sickle cell anemia and chronic ulcerations of the legs can be cited. A study of their case histories, however, shows that the initial episode occurred a number of [17] or many years [18] prior to the time of presentation. Nevertheless, because of the occasional case in which sickle cell ulcers may not be exhibited until the early thirties (as in our patient) or the late thirties,[19] this blood dyscrasia must be included in a consideration of the differential diagnosis of leg ulcers in middle-aged as well as in young Negroes.

In view of the absence of a familial history of hemolytic anemia in Case 2 (although one cannot be sure that the family history in this case was entirely reliable), there may be some doubt as to whether this patient suffered from congenital hemolytic icterus or from acquired hemolytic anemia. Since splenomegaly, spherocytosis, and increased fragility of the red blood corpuscles are common to the

16. The association of small, cherry red, papular hemangiomas with polycythemia vera has been noted by Wiener (Wiener, K.: Skin Manifestations of Internal Disorders [Dermadromes], St. Louis, C. V. Mosby Company, 1947, Chap. 33, p. 546).

17. Ebert, M. H.: Sickle Cell Anemia with Ulcer of the Left Ankle, Arch. Dermat. & Syph. **44**:948-949, 1941.

18. Steinfeld, E., and Klauder, J. V.: Sickle-Cell Anemia, M. Clin. North America **10**:1561-1576, 1927.

19. Smith, E. M., Jr., and Lewe, I. A.: Sickle Cell Anemia Associated with Chronic Ulcers of the Leg and Hyperkeratotic Plaques, Arch. Dermat. & Syph. **44**:946-947, 1941.

two conditions, a differential diagnosis is not possible on the basis of these findings alone. Our study antedated the Coombs test, which is now used to differentiate between congenital hemolytic icterus and acquired hemolytic anemia.[20] Although this test is generally positive in acquired hemolytic anemia and negative in the congenital forms (as in Case 3), positive reactions in special circumstances are occasionally obtained in the latter. To our knowledge, no instance of chronic leg ulcer associated with acquired hemolytic anemia has been recorded to date.

Most of the patients with congenital hemolytic icterus and leg ulcers reported prior to 1936[21] were German or Scandinavian women in their late teens or early twenties. More recent publications show that the ulcers may occur in older persons and that they may recur or persist for years.[22] Since our patient (Case 2) was in her early sixties and presented signs and symptoms of arteriosclerosis obliterans as well as of hemolytic icterus, it is difficult to say which of these two possible pathogenic factors, or whether or not both, contributed to the development of bilateral ulcerations in her case. The presence of epitheliomatous changes of the ulcer over the right ankle may be attributable to chronic local irritation, for malignant changes are known to develop in some long-standing ulcers.[22a] Awareness of the association of congenital hemolytic icterus with chronic or recurrent leg ulcers and early diagnosis of the disease are particularly important, since splenectomy effects a cure in the majority of cases.

The apparent late onset of the anemia in Case 3 places this case in the group of the so-called "mild" forms of Cooley's anemia, the course of which is less rapid, allowing patients to reach adult age.[23] Estes, Farber, and Stickney[8] regarded the dense deposits of iron in the cutis in the sections of the ulcer in one of their cases of Cooley's anemia as of "considerable interest." They referred to Whipple and Bradford[24] who considered iron-containing pigment in the organs of patients with Mediterranean anemia a characteristic feature of the disease. The potassium ferrocyanide test for hemosiderin in our case of Cooley's anemia (Case 3) likewise elicited a striking Perl reaction. A wide zone of purpura surrounding the ulcer was noted in addition to microscopic deposits of blood pigment in the histologic sections. The latter finding can hardly be regarded as specific, for Milne[25] has shown that the skin of the legs in older persons and in the region of old scars or trauma often contains deposits of hemosiderin.

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20. Singer, K., and Motulsky, A. G.: The Developing (Coombs) Test in Spherocytic Hemolytic Anemias: Its Significance for Pathophysiology of Spherocytosis and Splenic Hemolysis, J. Lab. & Clin. Med. **34**:768-783, 1949.

21. Taylor, E. S.: Chronic Ulcer of the Leg Associated with Congenital Hemolytic Jaundice, J. A. M. A. **112**:1574-1576, 1939.

22. Leger, L. H., and Orr, T. G.: Chronic Leg Ulcerations in Congenital Hemolytic Jaundice, South. M. J. **33**:463-464, 1940. Gentile, A.: Splenomegaly with Hemolytic Jaundice and Bilateral Leg Ulcers, Virginia M. Month. **72**:484-487, 1945.

22a. Mackee, G. M., and Cipollaro, A. C.: Cutaneous Cancer and Precancer: A Practical Monograph, New York, Am. J. Cancer, 1937, p. 85.

23. Chini, V., and Malaguzzi Valeri, C.: Mediterranean Hemopathic Syndromes, Blood **4**:989-1013, 1949.

24. Whipple, G. H., and Bradford, W. L.: Mediterranean Disease—Thalassemia (Erythroblastic Anemia of Cooley): Associated Pigment Abnormalities Simulating Hemochromatosis, J. Pediat. **9**:279-311, 1936.

25. Milne, J. A.: Pigmentation of Skin, Glasgow M. J. **30**:288-283, 1949.

Two cases of polycythemia with leg ulcers have been presented: one of polycythemia vera (Case 4) and one of symptomatic polycythemia (Case 5) secondary to pulmonary fibrosis.[26] A careful study of the peripheral circulation in Case 4 failed to disclose any evidence of peripheral vascular disease. Although the leg ulcer preceded the ulcerations on other parts of the body, the pathogenesis undoubtedly was the same for all the lesions. Malnutrition or trophic disturbances secondary to nervous system involvement were entertained as probable causes. In Case 5, the leg ulcer was attributable to thrombophlebitis of the superficial veins.

Peripheral vascular complications in polycythemia are not uncommon and occur in the symptomatic [5a] as well as in the idiopathic forms of the disease. One out of every 3 patients in a group of 100 with polycythemia vera studied by Brown and Giffin [27] and 9 of a group of 31 patients studied by Zeiter [5b] suffered peripheral vascular accidents. Migrating phlebitis,[28] thrombophlebitis, erythromelalgia, vasospastic neuroses, symptoms simulating or indistinguishable from thromboangiitis obliterans, arteriosclerosis obliterans, and Raynaud's disease are among the vascular changes that have been described.

Various hypotheses have been proposed to explain the association of leg ulcers with the blood dyscrasias. Gendel [2] was of the opinion that hypersplenism may be the common denominator in the diverse conditions represented. The association of chronic ulcerations of the leg and splenomegaly has also been noted by others,[29] although no explanation of the mechanism could be offered. Enlargement of the spleen was noted in each of the cases of hemolytic anemia presented in this paper and in one of the two cases of polycythemia. Granted that the association of chronic ulcers of the leg with splenomegaly seems too frequent to be coincidental, one cannot ascribe too much significance to this finding, since there are many more examples of splenomegaly unattended by leg ulcers.

The importance of occlusive arterial disease [5a] and of thrombophlebitis of the superficial vessels [28] in the development of leg ulcers in polycythemia has been well established. The pathogenesis of this cutaneous manifestation in the congenital hemolytic anemias, however, remains obscure.

SUMMARY

The cases of five patients with blood dyscrasias who sought dermatologic care because of chronic leg ulcers are presented. The hematologic entities represented in this group are 1 case of sickle cell anemia, 1 case of Mediterranean anemia, 1 case of congenital (?) hemolytic icterus, and 2 cases of polycythemia. These cases are described in detail, and the importance of a consideration of the blood dyscrasias in the differential diagnosis of leg ulcers is emphasized.

Dr. Charles F. Sims made the histologic studies of the ulcers.

26. Coope, R.: Diseases of the Chest, Ed. 2, Edinburgh, E. & S. Livingstone, 1948, Chap. 23 pp. 362-364.

27. Brown, G. E., and Giffin, H. Z.: Peripheral Arterial Disease in Polycythemia Vera, Arch. Int. Med. **46**:705-717, 1930.

28. Lüdeke, H.: Thrombophilie und Polycythämie, Arch. path. Anat. u. Physiol. **293**:218-251, 1934.

29. Witts, L. J.: Chronic Leg Ulcer in Purpura Hemorrhagica, Brit. M. J. **2**:309-310, 1942. Polson, C. J.: Chronic Leg Ulcer in Myelogenous Reticulosis, ibid. **2**:481-482, 1942.

NATURAL STEROID COMPLEX ("MARISONE") IN TREATMENT OF CUTANEOUS DISEASES

AARON D. SPIELMAN, M.D.
NEW YORK
AND
ALBERT BLAU, M.D.
BROOKLYN

THE HORMONES corticotropin and cortisone have proved helpful in several diseases of the skin, notably acute lupus erythematosus disseminatus, pemphigus, scleroderma, psoriasis, atopic eczema, and chronic urticaria.[1] The beneficial effects, however, last as long as the hormones are administered, and, furthermore, there are many undesirable and serious side-effects. They are expensive.

Recently, "marisone," a new drug for investigational use, became available. It is a steroid complex derived from pregnant mares' urine and from which the estrogenic conjugates have been removed.

Jaros and Spielman[2] have shown that "marisone" was well tolerated and is nontoxic when administered for prolonged periods in cases of bronchial asthma. "Marisone" was found to decrease the blood eosinophilia, increase the vital capacity, and clinically affect the asthma favorably. Its effects were therefore similar to those of the adrenal corticoids. We therefore decided to try "marisone" in those dermatoses that were reported to be favorably affected by the steroid hormones. In view of the work of Jaros and Spielman, we were especially interested in the effects of "marisone" in atopic eczema and urticaria. In evaluating the effects of "marisone" in the latter two diseases, it was necessary to take into consideration the well known emotional and neurogenic factors. Emotional conflicts often acted as trigger mechanisms to precipitate exacerbations and recurrences. Adrenal corticoid hormones play important roles in overcoming the "alarm" state; perhaps "marisone" is effective here because of a similar role. The patients with atopic eczema had been under treatment for many years, with the usual poor results.

METHOD

Thirty-one patients from the Dermatological Service of the Brooklyn Jewish Hospital, Kings County Hospital, and private practice were treated with "marisone." All other forms of therapy were discontinued during this period. There were eight cases of atopic eczema, seven of chronic or recurrent urticaria, six of acute urticaria following the use of penicillin,

1. Wolf, J.: Atopic Dermatitis: Some Aspects and Considerations, New York J. Med. **51**:1995 (Sept.) 1951. Cooke, R. A., and others: ACTH and Cortisone in Allergic Diseases: Clinical, Serologic (Electrophoretic), and Immunologic Studies, J. Allergy **22**:211 (May) 1951. Costello, M. J.: Cortisone in the Treatment of Cutaneous Diseases, New York J. Med. **51**:2017 (Sept.) 1951. Friedlaender, S., and Friedlaender, A. S.: Oral Cortisone Therapy in Allergic Diseases, J. Allergy **22**:291 (July) 1951.

2. Jaros, S. H., and Spielman, A. D.: Natural Steroid Complex in the Treatment of Bronchial Asthma, Ann. Allergy **9**:308 (May-June) 1951.

two of contact dermatitis, two of psoriasis, one each of exfoliative dermatitis, dermatomyositis, pemphigus, dermatitis herpetiformis, generalized erythroderma and dermatitis factitia. The usual dose was 1 capsule of 200 mg., five times a day for adults. In a few cases, the dose was increased to 8 capsules a day. In children, 3 capsules a day were used. No case was included in which marisone was used for less than 15 days. Twenty-two patients were females; 9 were males. Fourteen patients were 6 to 20-years-of-age, 16 patients were between 20 and 40-years-of-age and 1 was 60-years-old.

RESULTS

The first sign of improvement was subjective, a cessation of pruritus. Mothers reported that their children no longer scratched while they slept. The improvement was first noticed within four to seven days. This was followed by a clearing up of the secondary infection that was frequently present in the atopic eczemas. The lesions became dry and then the lichenifications began to abate. In cases of urticaria fewer wheals appeared and soon they ceased. Patients designated as having chronic urticaria had been having recurrent lesions for four to eight months. In those cases designated as having excellent or good results, not only were the subjective and objective results satisfactory to us but also to the patients and their parents. In eight cases of atopic eczema of long standing the results were very good in six and moderately good in two. After cessation of therapy there was no relapse for about three weeks. Reinstitution of the medication resulted again in the same good effects. In seven cases of long-standing recurrent urticaria there was a complete cessation of new lesions in four, appearance of a few lesions in two, and only slight improvement in one. In six cases of postpenicillin urticaria (four in syphilitic patients) the condition usually cleared in 48 hours. Two lasted from four to six days. In two cases of contact dermatitis there was good improvement in one and very little in the other. In these cases, of course, the patients were no longer in contact with the offending substances. In a case of generalized erythroderma of undetermined origin there seemed to be satisfactory improvement for several weeks, but the patient was lost to observation because of cardiac failure and hospitalization elsewhere. In two cases of psoriasis and one each of exfoliative dermatitis, dermatomyositis, dermatitis herpetiformis and dermatitis factitia the eruption seemed to be uninfluenced by "marisone."

SIDE-EFFECTS

The only side-effect that could be attributed unequivocably to "marisone" was enlargement of the breasts of a 6-year-old boy. This boy, who had had atopic eczema for almost his entire life, obtained very good therapeutic results. After about two weeks of treatment, bilateral painless enlargement of the breasts was noted. Treatment was stopped and the enlargement completely disappeared within three weeks. Use of "marisone" was then resumed. In about three weeks swelling of the breasts returned, and again returned to normal within three weeks after stopping of the treatment. A return of itching occurred two weeks after cessation of medication. In a 60-year-old woman questionable enlargement of the breasts developed eight weeks after the start of "marisone" therapy.

A 24-year-old woman acquired a generalized morbilliform eruption three days after administration of "marisone" was begun. She had psoriasis of many years' duration. However, this case was complicated by the fact that she was under treatment for syphilis at the same time and was receiving penicillin.

A 48-year-old man with urticaria and serum sickness had an acne-like eruption on his face on the fifth day of treatment; it disappeared when treatment was stopped. Two patients, both with a long-standing history of atopic dermatitis, stated upon questioning that their menstrual periods were delayed. The use of "marisone" was not stopped by these patients, and menstrual periods of normal character came on in the midst of therapy but apparently late.

COMMENT

Our results with "marisone," a natural steroid complex, in the treatment of atopic dermatitis and urticaria were impressive. Discussion of the effect of "marisone" in the other dermatoses is not warranted because of the small number of cases in each category. The results in general were unsatisfactory. This natural steroid complex appears to be safe and well tolerated, with few important side-effects.

The action of "marisone" in reducing eosinophile cells in the peripheral blood and the lack of inhibition of skin reagins, is similar to reactions observed following the administration of other adrenal corticoids. "Marisone" may contain steroids which act as precursors or direct replacements for enzyme-activating steroids which cause relief of the persistent pruritus.

When improvement occurred, it was noted after four days of treatment. There was striking relief from itching. After cessation of therapy the clinical benefits persisted for at least two weeks—in some cases as long as four weeks. Prolonged uninterrupted administration was well tolerated (one patient has taken "marisone" for 120 days). For adults, the optimal dosage was 1 gm. a day. After three weeks of administration, a rest period of two weeks may be given without relapse. The only side-effect that we are sure is related to the use of "marisone" is enlargement of the breasts. This is reversible with withdrawal of the medication. Possibly the acne-like eruption is related to "marisone" administration. Whether the "marisone" was related to the delayed menstruation is questionable.

CONCLUSIONS

1. "Marisone," a natural steroid complex, proved beneficial in the treatment of atopic dermatitis and in chronic urticaria. It seemed to shorten the course of acute urticaria. In two cases of contact dermatitis, in two cases of psoriasis, and one case each of exfoliative dermatitis, dermatomyositis, pemphigus, dermatitis herpetiformis, generalized erythroderma, and dermatitis factitia, "marisone" was apparently ineffective.

2. The compound is well tolerated and produces few reactions. These are reversible with cessation of treatment.

3. Clinical experience indicates that "marisone" is a useful adjuvant in therapy of atopic dermatitis and of acute and chronic urticaria.

ANAPHYLAXIS FROM PENICILLIN

Report of a Case

GEORGE M. STROUD, M.D.
CLEVELAND

THIS ARTICLE was written to indicate the successful treatment of a case of anaphylactic shock from a new drug, *l*-ephenamine penicillin G (compenamine [1®]), which had been reported by Longacre [2] and Kadison and others [3] to have been less allergenic than standard preparations.

REPORT OF CASE

At 11:10 p. m., on Jan. 18, 1952, a 47-year-old physician suddenly became weak, pale, and cyanotic within a minute after a nurse injected (without preliminary aspiration) 300,000 units of *l*-ephenamine penicillin in aqueous suspension in his gluteal region because of asthmatic bronchitis which had developed four days previously. In about two minutes he was given 1.0 cc. of 1:1,000 epinephrine hydrochloride solution subcutaneously. Within a matter of seconds he became comatose, but in another two or three minutes he was alert again. At this point I arrived and found a well-developed, heavy-set man lying on the floor, pale, cold, cyanotic, sweaty, and barely able to move a muscle. He asked for and received 0.5 cc. of epinephrine subcutaneously. This was repeated four times at his request at intervals of two to five minutes because it relieved a severe tight feeling in his chest and enabled him to breathe more easily. He was also given 150 mg. of cortisone intramuscularly. He was then quickly transported by ambulance to St. Luke's Hospital in Cleveland.

On the patient's arrival in the accident ward, the signs of shock were the same as before. The skin had a marked "goose flesh" appearance. The pulse was barely perceptible. The heart sounds were of fair quality but rapid in rate. The blood pressure was 60/40. In the lungs a few fine moist rales and distant breath sounds were noted. Five-tenths cubic centimeter of epinephrine was injected subcutaneously on four occasions, when requested, within a half-hour and 40 mg. of corticotropin (ACTH) was injected twice intramuscularly.

At this point an allergist arrived and took charge. After evaluating the situation, he administered 0.26 gm. of aminophylline, which considerably eased the substernal oppression but was followed by numbness, particularly in the hands and feet. This sensation was counteracted by another injection of epinephrine and administration of oxygen at the rate of 7 liters a minute. Slowly the patient's color, pulse, and strength improved, and his blood pressure rose to 110/60 at 1:15 a. m. on Jan. 19.

He was then transferred to a private room and had a mild chill for 20 minutes and nausea. However, at 2:30 a. m. he was considerably stronger but still felt slight tightness in the thorax. Nasal administration of oxygen was continued for approximately 36 hours. From then

Senior Clinical Instructor in Dermatology and Syphilology, Western Reserve University Medical School; Assistant Dermatologist and Syphilologist, University Hospitals of Cleveland.

1. Manufactured by C. S. C. Pharmaceuticals (a division of Commercial Solvents Corporation), 17 E. 42d St., New York 17.

2. Longacre, A. B.: Compenamine: Report of a Very Low Reaction Rate in Therapy with a New Penicillin Salt, Antibiotics & Chemother. **1**:223 (July) 1951.

3. Kadison, E. R.; Ishihara, S. J., and Waters, T.: A New Form of Penicillin with Anti-Allergic Properties, Am. Pract. & Digest. Treat. **2**:411 (May) 1951.

on, the chest oppression slowly went away. The temperature fell slowly from 38.0 C. (100.4 F.) to 37.0 C. (98.6 F.) six days later. Twelve hours after admission, his pulse rate was 120. In 24 hours, it dropped to 72.

A cardiologist checked his heart after the acute symptoms subsided, on Jan. 19, and found no evidence of disease. After the patient returned home, on the sixth day, he had slight transient swelling of the lips. He was considerably weak for ten days but recovered completely in a month's time.

The family history was important because of the allergic manifestations of rhinitis in his mother and in a paternal cousin. The patient had had recurrent urticaria from certain foods and pruritus of the legs when tripelennamine (pyribenzamine®) hydrochloride was taken for sinusitis and asthmatic bronchitis. Eighteen months before this episode following an intramuscular injection of 300,000 units of aqueous procaine penicillin, he had a sudden attack of nausea and vomiting lasting for five minutes. Prior to this he had had about 10 injections of penicillin and had consumed about 10 tablets over a three-year period.

A blood examination on Jan. 19, showed 16.8 gm. of hemoglobin per 100 cc., 5,800,000 erythrocytes per cubic millimeter and 13,000 leucocytes, of which 3% were eosinophiles. Two days later, 24% of the 14,000 leucocytes were eosinophiles. An x-ray picture of the chest showed no abnormality. The electrocardiogram was normal.

COMMENT

No reports were found of anaphylaxis from *l*-ephenamine penicillin. However, there have been nine cases of anaphylaxis from other types of penicillin recorded since 1947. These were described by Sawicky and Rein,[4] Waldbott,[5] Burleson,[6] Léchelle and Chapuis,[7] Corajod and others,[8] Everett,[9] and Irwin and others,[10] and mentioned in a personal communication by Criep.[11] Shock occurred within several minutes in six cases and within 15 to 30 minutes in the other three.

I was greatly aided by the patient's specific requests for, and the indications of, relief from epinephrine, total of 5.5 cc. The patient was comforted by this drug and, interestingly, had no side-effects. Oxygen therapy was considered subjectively by the patient to have given him a definite boost toward recovery, which was substantially under way within three to four hours. No immediate effect was noticed or expected from cortisone or corticotropin. In the course of therapy, diphenhydramine (benadryl®) hydrochloride was considered for intravenous use, but was not given because it was regarded as a potential sensitizer, whereas epinephrine was not and was effective.

Intramuscular injection of pyrilamine (neo-antergan®) maleate did not protect the patient reported by Léchelle and Chapuis [7] from circulatory shock. In Corajod's [8]

4. Sawicky, H. H., and Rein, C. R.: Severe Reactions to Penicillin, Arch. Dermat. & Syph. **58**:83 (July) 1948.

5. Waldbott, G. L.: Anaphylactic Death from Penicillin, J. A. M. A. **139**:526 (Feb. 19) 1949.

6. Burleson, R. J.: Anaphylactoid Shock Due to Penicillin: Report of a Case, J. A. M. A. **142**:562 (Feb. 25) 1950.

7. Léchelle and Chapuis: Accidents dus à l'usage d'une variété déterminée de pénicilline, Bull. et mém. Soc. méd. hôp. Paris **66**:510, 1950.

8. Corajod, E.; Fournel, and Chatillon: Shock anaphylactique morel dû à la pénicilline, Acta chir. belg. **50**:299-303 (May) 1951.

9. Everett, R.: Anaphylactic Reactions from Local Use of Penicillin: A Report of 2 Cases, J. A. M. A. **146**:1314 (Aug. 4) 1951.

10. Irwin, J. W.; Graham, A. B.; Jacobson, B. M., and Burrage, W. S.: Penicillin Allergy, New England J. Med. **245**:246 (Aug. 16) 1951.

11. Criep, L.: Personal communication to the author.

case, the first two major episodes of anaphylaxis were treated effectively with intravenous ethyl phenothiazine (phenergan®) hydrochloride and a phenothiazine-procaine compound. The patient went into shock a third time and died despite intravenous phenothiazine, intracardiac epinephrine and cardiac massage. In Burleson's [6] case of severe anaphylaxis there was response within 10 minutes to 30 to 40 mg. of diphenhydramine intravenously, given rapidly over 60 seconds. A relapse in 45 minutes which subsided spontaneously suggested that the dose should have been repeated. Most of the patients who survived responded to the standard physical methods of treating shock, supplemented by a single injection of epinephrine, and ingestion of an antihistamine drug.

Waldbott [5] in 1949 reported the first death from penicillin anaphylaxis. Corajod's [8] case was the only other case of this reaction found in the literature. However, Dr. Leo Criep has added a third case.

A young girl who had received penicillin previously and decided to give herself an injection of penicillin in the thigh. She was a nurse on night duty, and died within minutes after the injection of penicillin. The post-mortem was done and revealed some edema of the lungs but no other findings. . .

SUMMARY

As far as can be determined the case reported is the first instance of anaphylactic shock from *l*-ephenamine penicillin (compenamine®). A considerable number of doses of epinephrine were effective in relieving the severe tightness in the chest and enabled the patient to breathe easier. Oxygen therapy aided recovery.

ERYTHEMA GYRATUM REPENS

Skin Manifestations in Patient with Carcinoma of Breast

JOHN A. GAMMEL, M.D.
CLEVELAND

THE DERMATOLOGIST of the twentieth century has been trained to consider the possibility of internal diseases in all cases of atypical, bizarre, or recalcitrant dermatoses. As skin lesions are frequently the first signs of various types of malignant lymphoma, he is often in a position to suspect these fatal diseases before a clinical or laboratory diagnosis is possible. The association of acanthosis nigricans and visceral cancer is well known, as are metastases to the skin from internal cancers. Other skin eruptions have been observed in the presence of cancer and sarcoma, but they are rather rare. In some instances they may have been coincidental; in others a causal relationship is almost certain. In most cases the patients came first to the dermatologist, who later referred them to the surgeon or roentgenologist.

REVIEW OF LITERATURE

In 1925 Rothman [1] wrote a comprehensive review on the subject of cutaneous manifestations in patients with malignant tumors and added three observations of his own. In 1942 Becker, Kahn, and Rothman [2] reported two more cases and collected eight from the literature [3] since Rothman's essay.[1] Wiener,[4] in his textbook, devotes one chapter to dermadromes due to cancers. I found a few additional reports, but for the sake of brevity and to avoid duplication I wish to review only those cases in which skin lesions disappeared after removal of the cancer and thus a reasonable proof of their relationship to the internal neoplasm could be established.

The credit for having reported the first case belongs to Blaschko.[5] His patient was a 22-year-old man with a lymphosarcoma in the supraclavicular fossa. After

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From the Department of Dermatology and Syphilology of Western Reserve University and University Hospitals of Cleveland, service of Dr. H. N. Cole.

1. Rothman, S.: Über Hauterscheinungen bei bösartigen Geschwülsten innerer Organe, Arch. Dermat. u. Syph. **149**:99-123, 1925.

2. Becker, S. W.; Kahn, D. and Rothman, S.: Cutaneous Manifestations of Internal Malignant Tumors, Arch. Dermat. & Syph. **45**:1069-1080, 1942.

3. The case of Beron (presented before the Bulgarian Dermatological Society on April 20, 1929) does not seem to belong to this category and impresses me as an instance of true pellagra in a patient with carcinoma of the stomach (Beron, B.: Pellagroide Hautveränderungen und Magencarcinoma, Zentralbl. Haut- u. Geschlechtskr. **35**:457, 1931).

4. Wiener, K.: Skin Manifestations of Internal Disorders (Dermadromes), St. Louis, C. V. Mosby Company, 1947, pp. 569-571.

5. Blaschko: Case Presentation, Dermat. Ztschr. **7**:250-251 and 820-823, 1900.

relative quiescence for three years the tumor spread rapidly, and at the same time a violent general pruritus developed. There were deep excoriations and on the lower extremities a few small pruritic nodules. After removal of the tumor, the pruritus stopped suddenly and only a few pigmented spots remained. Several months later the sarcoma recurred and with it intolerable itching. Blaschko assumed that toxic products of the tumor caused the pruritus, especially since necrosis was present. It was not until 23 years later that Drew [6] actually proved by means of tissue cultures that tumors do produce toxic substances.

Another classic example is that of Bogrow.[7] The patient was a 28-year-old Russian peasant woman who suffered from a gradually spreading eruption of two months' duration. The eruption was polymorphous and consisted of grouped vesicles and urticaria-type papules. There were pruritus and eosinophilia (35.4%). A diagnosis of dermatitis herpetiformis was made. Gynecological examination revealed a massive carcinoma originating in one labium. The tumor and the portio vaginalis were extirpated, and the wound was closed. Three days after the operation the vesicles had dried up and were replaced by bluish macules. There were pigment spots all over the body. The eosinophile count dropped to 6.6%. An examination four weeks later showed a recurrence of the carcinoma. The patient died after four months without a recurrence of the dermatitis. The author ascribed the absence of the recurrence of the eruption to the lack of necrotic tissue in the recurrent carcinoma.

In 1922, Davis [8] reported on two cases of exudative erythema associated with cancer of the uterus. One patient had a spindle cell sarcoma. The eruption cleared up shortly before death. In the other patient, curettage revealed adenocarcinoma and the skin lesions disappeared after hysterectomy.

Usland [9] observed a patient with generalized pruritus of nine months' duration. Skin manifestations developed which suggested dermatitis herpetiformis and acanthosis nigricans. The patient had a scirrhus ventriculi with minimal necrosis. One month after the resection of the tumor, the eruption had disappeared.

Schweigl [10] reported in 1933 on erythroderma generalisata exfoliativa subacuta of several months' duration in a patient with uterine carcinoma. Three weeks after the operation the eruption, which previously had resisted all therapeutic efforts, had cleared up completely.

Elliott [11] in 1938 described a case of dermatitis-herpetiformis-like process considered as herpes gestationis in a woman with choriocarcinoma. Removal of the tumor resulted in prompt disappearance of the skin lesions.

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6. Drew: Investigations of the Imperial Cancer Research Fund, 1923, p. 33, cited by Rothman.[1]

7. Bogrow, S. L.: Zur Kasuistik der Dermatitis herpetiformis Duhringi, Arch. Dermat. u. Syph. **98**:327-334, 1909.

8. Davis, H.: Two Cases of Exudative Erythema Associated with Malignant Disease of the Uterus, Brit. J. Dermat. **34**:12-16, 1922.

9. Usland, O.: Hautausschlag als praemonitorisches Symptom bei Magenkrebs, Med. rev., Bergen **44**:13-23, 1927; abstracted, Zentralbl. Haut- u. Geschlechtskr. **24**:369, 1927.

10. Schweigl, R. L.: Erythrodermie und Uteruskarzinom, Zentralbl. Gynäk. **57**:94-99, 1933.

11. Elliott, J. A.: Bullous Dermatoses of Toxic Origin: Report of a Case Involving an Association with Choriocarcinoma, Arch. Dermat. & Syph. **37**:219-233, 1938.

In 1942 Urbach [12] mentioned shortly two cases of persistent urticaria. In one a hydatiform mole was discovered, and a complete cure followed removal. In the same article Urbach showed a picture of a 70-year-old man with urticarial exanthema which disappeared after extirpation of a cancer of the rectum.

In 1949 Siegel [13] reported the case of a bullous eruption associated with carcinoma of the penis. The eruption cleared after high voltage irradiation of the tumor. The patient died five months later, but the cutaneous lesions had not recurred. Since he gave a history of previously having had two attacks of bullous eruptions considered as "poison ivy" dermatitis, the relationship to the tumor is somewhat problematical.[14]

In 1951 Tobias [15] published a case of dermatitis herpetiformis which disappeared after the removal of a papillary carcinoma of the right ovary. There were also present chronic cervicitis, fibromas, and numerous small cysts of the cervix. The tumor recurred but not the eruption.

REPORT OF A CASE

An 11th case similar to those enumerated was observed by me. Since it showed unusual clinical features and the patient survived, it is deemed worthy of publication.

History.—Mrs. L. O. was born May 29, 1892. She was first seen in my office on April 17, 1948. Her father had died of cancer at the age of 70. Her 80-year-old mother was in good health. One sister had been operated on for carcinoma of the breast. The patient had a hysterectomy and oophorectomy 10 years previously. Her general health was good except for insomnia. There was no history of previous skin diseases. Her husband died suddenly in July, 1947, during an abdominal operation.

About three weeks later, the patient noticed a pruritic area on the anterior surface of the neck and upper part of the chest followed by scaling. An eruption developed gradually and spread until it involved the entire trunk, and to a less degree the extremities. The eruption on some parts seemed to clear up, while that on others flared up. At no time since its onset was the patient free from skin manifestations. From September, 1947, to January, 1948, she treated herself with calamine lotion with phenol. In February and March, 1948, she received seven x-ray treatments given by a dermatologist who suspected a phenolphthalein eruption. In the early part of April, an acute dermatitis developed on the neck and spread to the face, scalp, and ears. Careful questioning of the patient did not reveal the ingestion of drugs other than an occasional proprietary laxative.

Physical Examination.—On the first examination, the face and neck of the patient were found reddened and scaly. There was edema of the eyelids with small fissures and some exudation. The conjunctivae were injected. The ears were moderately swollen, exuding in places, scaly in others. A pruritic scaly erythema extended well into the scalp.

The entire trunk and both arms and legs showed erythema in irregular wavy bands with collarette-type, or marginal, desquamation. These bands showed a peculiar gyrate or serpiginous outline. The configuration of the erythema resembled somewhat the graining of a knotty cypress

12. Urbach, E.: Endogenous Allergy, Arch. Dermat. & Syph. **45**:697-722, 1942.

13. Siegel, J. M.: A Bullous Eruption Associated with Carcinoma of the Penis, Arch. Dermat. & Syph. **59**:659-661, 1949.

14. Loewe, L., and Camiel, M. R.: Exanthem Complicating Neoplastic Disease, Am. J. Roentgenol. **43**:587-596, 1940. These authors reported 4 cases of exanthema which occurred after deep irradiation of tumors and assumed that cellular decomposition may have caused an allergic or toxic reaction. Eruptions after deep irradiation of malignant tumors have been observed by several authors.

15. Tobias, N.: Dermatitis Herpetiformis Associated with Visceral Malignancy, Urol. & Cutan. Rev. **55**:352, 1951.

board. There was blanching under light pressure. The erythema moved constantly at the rate of about 1 cm. per day. Within a few days there was linear desquamation. The hands and the feet were free. There was a large lymph node palpable in the left axilla and smaller ones in the groin.

Fig. 1.—Changes in the appearance of the skin lesions within five days. The configuration resembles the grain of a wooden panel. The pictures on the left taken on May 3, 1948; those on right, on May 8.

The patient was admitted to the University Hospitals on April 23 for further study. The condition of the integument was essentially the same as six days before. The heart was not enlarged. There was a systolic murmur at the apex and in the aortic area. The blood pressure was 140/70. There was an umbilical hernia with serous discharge from the umbilicus. The patient complained of pruritus vulvae and a fairly thick vaginal discharge. The urine was nor-

mal. The blood urea nitrogen was within normal limits. The hemogram showed 4,200,000 erythrocytes and 4,210 leucocytes per cubic millimeter. The hemoglobin content was 82%. The differential blood count showed 57% neutrophiles, 40% lymphocytes, 2% mononuclear cells and 1% eosinophiles. The temperature was not elevated. The Wassermann and Kline reactions were negative. There was some occult blood in the stool but no pathological findings on microscopic examination. No fungi were found in the scales by direct examination or in cultures.

The roentgenogram revealed no abnormalities in chest, mediastinum, or bony thorax. Roentgenograms of teeth showed only the upper first right premolar tooth devitalized. There was no evidence of retained root fragments or periapical abscesses.

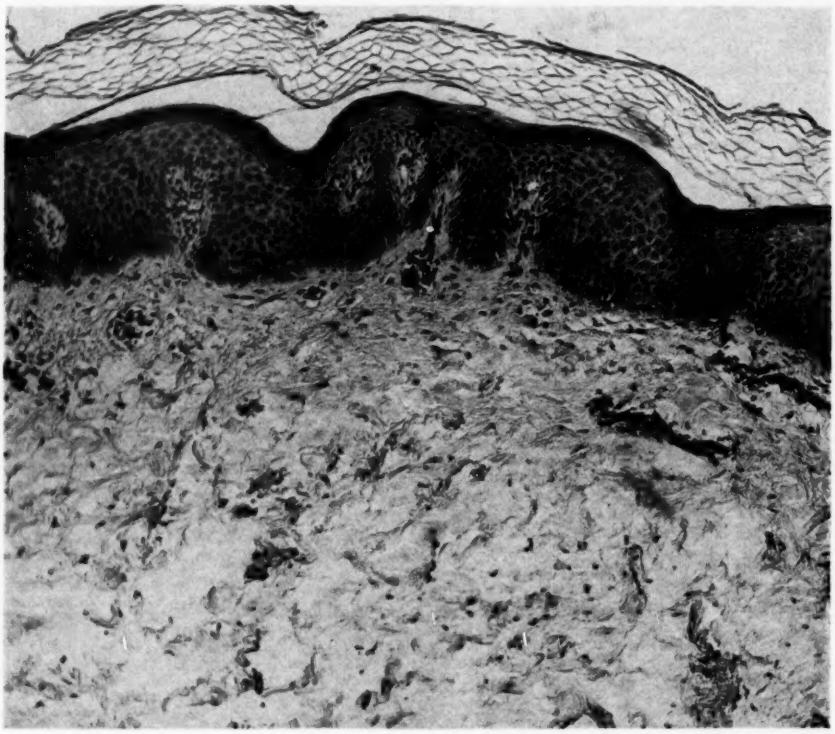

Fig. 2.—Section of skin from lesion on abdomen. The stratum corneum consists of loose laminae of keratin. There is moderate acanthosis and perivascular infiltration in the upper cutis. Some lymphocytes and lymphoid cells are scattered in the slightly edematous connective tissue.

The patient received diphenhydramine (benadryl®) hydrochloride, 50 mg. every four hours during the day; boric acid compresses to the eyes, and 0.25% zinc sulfate eye drops. Locally to some parts, cold cream with menthol was applied, to others olive oil with 2% salicylic acid and 3% juniper tar. There was no improvement under this regimen. A biopsy specimen was taken on April 28, 1948, and an axillary lymph node was excised on May 10. Frozen sections of the latter showed carcinoma. A small nodule, less than 2.5 cm. in diameter, was discovered in the depth of the left breast. The following day a radical mastectomy was done with the patient under general anesthesia (nitrous oxide and ether) by Dr. Frederick R. Mautz. The pathological diagnosis was poorly differentiated adenocarcinoma of the breast with metastases to axillary lymph nodes; intraductal papilloma of the breast; abnormal cystic involution of the breast, and lipomelanotic reticulosis of axillary lymph nodes.

Histologic Examination of Skin (Dr. H. Z. Lund).—The stratum corneum was slightly thickened. It consisted of loose laminae of keratin. The epidermis was moderately acanthotic. In the upper cutis, especially in the papillary layer, there was a perivascular infiltrate of lymphocytes and small mononuclear cells with cytoplasmic processes (lymphoid cells). Similar cells were seen scattered in the connective tissue away from the capillaries, but they were sparse. The capillary endothelium was slightly hyperplastic. Occasionally the capillaries contained small mononuclear cells, probably lymphocytes and a few neutrophilic polymorphonuclear cells. There was slight dilatation of a few of the capillaries; others were collapsed. There was diffuse and moderate edema of the connective tissue.

A section of the nipple showed edema of the papillary layer and infiltration of cells similar to those mentioned before. The cells were not sharply confined to the pericapillary region. Occasional melanophores were present. The reaction was limited to the papillary and subpapillary layer. The changes were comparable with those given by Darier [16] in his description of erythema annulare centrifugum. In most sections the infiltrate was not so diffuse as that described by Butler.[17]

Forty-eight hours after the operation there was a marked improvement, and during the next 10 days the eruption cleared almost completely; however, mild attacks of transient gyrate erythema on forearms and abdomen occurred. The eruption on the face, scalp, and neck cleared without further medication. The white blood cell count rose to 7,950 per cubic millimeter after the operation but dropped back to 4,850 on the 12th postoperative day.

This patient was presented at the meeting of the Cleveland Dermatological Society on May 27, 1948. Only minimal linear exfoliation and a few fugacious bands of erythema less than 1 cm. wide could be shown. In the discussion the diagnosis of erythema annulare centrifugum was offered. Likewise, the possibility of psychosomatic influences or of a reaction to the anesthesia was considered.

Six weeks after the operation the last traces of the eruption were gone, and neither carcinoma nor skin manifestations have recurred in the past four years.

COMMENT

Rothman [1] classified the skin manifestations associated with internal cancers into four groups: (1) pruritus and a prurigo-like syndrome with hyperpigmentation; (2) toxic-bullous eruptions; (3) metastatic cutaneous lesions and inflammatory lesions preceding metastases, and (4) acanthosis nigricans and similar proliferative changes. To this may be added (5) urticaria and (6) erythema gyratum migrans.

Most dermatoses recorded were atypical and did not fit any definite clinical entity. Eruptions considered as dermatitis herpetiformis or at least suggesting this diagnosis were observed more frequently than any other type.[18] Urbach [12] reported urticaria, and Schmidt [19] observed a case of herpes zoster which cleared up within three weeks. However, the vesicles left papular infiltrates which eventually became metastatic carcinomas. In some cases there were several types of lesions. The most constant feature was severe pruritus.

Rothman [1] assumed that single tumor cells transported to the skin by the blood stream are decomposed in the skin, with accompanying local inflammation. The case

16. Darier, J.: De l'érythème annulaire centrifuge (érythème papulo-circiné migrateur et chronique) et de quelques éruptions analogues, Ann. dermat. et syph. **6**:57-76, 1916-1917.

17. Butler, J.: Erythema Annulare Centrifugum, Arch. Dermat. & Syph. **25**:111-121, 1932.

18. Rothman,[1] Bogrow,[7] Usland,[9] Elliott,[11] Tobias,[15] Harf, A.: Über Hauterscheinungen als Frühsymptome des Karzinoms, Zentralbl. Chir. **52**:2699-2701, 1925. Traub, E. F.: Dermatitis Herpetiformis: Cancer of Pancreas, Arch. Dermat. & Syph. **38**:974, 1938.

19. Schmidt, A.: Herpetische Eruptionen als Vorstadium eines Hautcarcinoms neben Herpes zoster, Arch. Dermat. u. Syph. **70**:321-328, 1904.

of Schmidt [19] seems to support this hypothesis and suggests that the tumor cells may also remain viable and cause metastases. Rothman [1] emphasized that in most cases there was necrosis or putrefaction in the primary malignant tumor. Absence of necrosis could explain the absence of the recurrence of the dermatitis herpetiformis in Bogrow's [7] case when the carcinoma recurred. Urbach [12] suspected that altered organ proteins acted as endogenous allergens. He admitted, however, that proof that the resorbed material acted as an allergen and not as a toxin, was lacking.

I am inclined to accept Urbach's theory. The disappearance of the eruption in a few cases prior to death could be explained as anergy. In my case, the eruption cleared up rapidly as soon as the carcinoma mammae and its metastases were removed. Yet mild new transient lesions appeared for a few more weeks, until they finally stopped altogether. It may be assumed that the disappearance of the skin lesions coincided with the elimination of the last carcinotoxins in the body. I regret that no experimental proof for this theory could be brought forth. A relationship to the carcinoma was not suspected until the eruption faded dramatically after the operation and the specimen was embedded in formalin for two days.

The peculiar gyrations, the ring formation, and the constant migration are perhaps hardest to explain. Proppe [20] calls this phenomenon perinomody and supposes it to be due to a specific biological mechanism hitherto unknown which must be distinguished from allergy and the Sanarelli-Shwartzman phenomenon. Allergic or traumatic factors certainly must start the process. Proppe [20] believes that the condition is a centrifugal, gradually extending alteration of the reactivity of a circumscript part of the skin. If Proppe's interesting theory is followed the eruption in my case is the resultant of an allergen and the condition of the "terrain," in this case the skin of the patient.

Prior to the operation my search was concentrated on the field of the rare erythemas. It would be beyond the scope of this short essay to discuss this subject comprehensively. I wish to present only a table of the more important erythemas described in recent decades.[21] A number of erythemas not included were reported shortly in the transactions of various local dermatological societies and were published only as titles or one-paragraph case reports.

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20. Proppe, A.: Perinomodia, das Phänomen des Abweidens, Dermat. Wchnschr. **120**:305-311, 1949. The word perinomodia derives from *νέμειν* "to graze." This root is used in noma. *Νομώδης* means "in the manner of the rodent ulcer," a term found in later Greek literature.

21. (*a*) Hebra.[25] (*b*) Fox.[22] (*c*) Lustgarten, S.: Erythema papulosum vel urticatum, figuratum, perstans et chronicum, J. Cutan. Dis. **11**:110, 1893. (*d*) Arning, E.: Ein Fall von Erythema perstans pseudoleprosum, Arch. Dermat. u. Syph. **43**:11-18, 1898. (*e*) Sachs, O.: Erythema exsudativum perstans, Verhandl. deutsch. dermat. Gesellsch. **7**:405-413, 1901. (*f*) Danlos, M. H.: Érythème annulaire et diabète, Bull. Soc. franç. dermat. et syph. **12**:212-213, 1901. (*g*) Finny, J. M.: Erythema marginatum perstans, Med. Press & Circ. **75**:51-53, 1903, cited by Wende, G. W.: Erythema Perstans, with Report of 2 Cases Involving Circinate Lesions, J. Cutan. Dis. **24**:241-251, 1906. (*h*) Bloch, M.: Érythème circiné recidivant (dermatite herpetiforme, variété erythemateuse?), Ann. dermat. et syph. **8**:126-129, 1907. (*i*) Wende.[23] (*j*) Lipschütz.[27] (*k*) Darier.[16] (*l*) Strempel, R.: Ein Fall von Erythema milkogyratum persistens, Dermat. Ztschr. **36**:63-70, 1922. (*m*) Jadassohn, J.: Erythema Simplex Gyratum, in Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Springer-Verlag, 1928, Vol. 6, Pt. 2, p. 656. (*n*) Gammel, J. A., and Marmelzat, W.: Erythema Gyratum Migrans: Psychosomatic Influences? Arch. Dermat. & Syph. **61**:526, 1950.

Even some of the erythemas tabulated are described so sketchily that it is not possible to evaluate them. Erythema gyratum perstans (Colcott Fox [22]), erythema figuratum perstans (Wende [23]), and Darier's 16 erythema annulare centrifugum must be considered most seriously in differential diagnosis.

Erythema gyratum perstans was seen by Fox [22] in two members of one family. It appeared in early childhood and was observed over decades. Scattered raised papules about the size of a millet seed quickly extended centrifugally. Often within a few hours erythematous rings were formed surrounding a slightly pigmented but otherwise normal skin. As the rings enlarged they met and fused, forming eventually large festooned or gyrate lesions. Shoulders, thighs, and buttocks were most

Data on Some of the Rare Erythemas

Type	Author	Comment
E. exudativum multiforme	Hebra,[25] 1854	Was known as E. marginatum, papulatum, tuberculatum (Willan), gyratum (Fuchs), annulatum, circinatum, centrifugum (Biett), E. iris (Rayer), herpes iris and herpes circinatus (Willan)
E. gyratum perstans	Fox,[22] 1881	Scattered papules, blanched under pressure, spread rapidly peripherally into large gyrate lesions, lasted decades
E. papulosum vel urticatum figuratum perstans et chronicum	Lustgarten,[21c] 1893	Annular and gyrate patches with elevated borders, remained for weeks and months, healed under pigment formation
E. perstans pseudoleprosum	Arning,[21d] 1898	Brownish livid patches with elevated borders on lower limbs, responded to chrysarobin
E. exudativum perstans	Sachs,[21e] 1901	Lenticular papules, formed rings of up to 10 cm. diameter in 8 to 10 days, borders hard, center depressed, lasted days, weeks, months
Érythème annulaire	Danlos,[21f] 1901	Diabetic patient with annular erythematous lesions, rings up to quarter size, 3 weeks' duration; Hallepeau diagnosed urticaria
E. marginatum perstans	Finny,[21g] 1903	Pinkish-red elevated lesions, linear, curved or segmentary on covered parts of body, some pigmentation and scaling
E. circiné recidivant	Bloch,[21h] 1907	37 years' duration; large symmetrical, circinate patches, each consisting of groups of circinate lesions
E. figuratum perstans	Wende,[23] 1906-1908	Circinate lesions, rapidly spreading to rings up to 15 cm. diameter; outer edges smooth, inner edges scaly, 4 to 16 years
E. chronicum migrans (persistens) (dermatitis migrans Afzelius '08)	Lipschütz,[27] 1914	One or two giant lesions with diameter of up to 50 cm.; virus infection? Allergic reaction to woodtick bite?
E. annulare centrifugum	Darier,[16] 1916	Polycyclic, annular or gyrate arrangement, keloid-like consistency, no scales, crusts or vesicles; asymptomatic
E. microgyratum	Strempel,[21i] 1922	Cinnabar lesions 5 to 30 mm. in diameter, became confluent, lasted several months; patient had ulcerative gingivitis
E. simplex gyratum	Jadassohn,[21m] 1928	No exudative phase or cyclic course, irregular localization, annular macules, no discomfort
E. gyratum migrans	Gammel,[21n] 1948	Widespread gyrate bands of erythema with linear desquamation, configuration resembling the grain of wood

affected. These exacerbations occurred at frequent but irregular intervals. Klaber [24] reported a case of the eruption in a 24-year-old woman. There was marked pruritus.

In Wende's patients the erythema figuratum perstans extended from 4 to 16 years. The lesions varied from 1 to 15 cm. in diameter. Gyrate lesions were elevated, slightly uneven, and bright to dull red. Pruritus was intense.

The reports on erythema annulare centrifugum were read in the original articles when available. Butler,[17] in his scholarly analysis of this morphologic entity, came

22. Fox, T. C.: Erythema Gyratum Perstans, International Atlas of Rare Skin Diseases, Pt. V, 1901, cited by Tachau [26] and Wende, W.: J. Cutan. Dis. **24**:241-251, 1906.

23. Wende, G. W.: Erythema Perstans with Report of 2 Cases Involving Circinate Lesions, J. Cutan. Dis. **24**:241-251, 1906; Erythema Figuratum Perstans, J. A. M. A. **51**:1936-1939, 1908.

24. Klaber, R.: Erythema Gyratum Perstans (Colcott Fox) : A Case Report, with Discussion on Relations with Erythema Centrifugum Annulare (Darier) and Dermatitis Herpetiformis, Brit. J. Dermat. **58**:111-121, 1946.

to the conclusion that too many conditions are included under this title. He believed that only those eruptions should be classified as Darier's erythema annulare centrifugum which show (1) polycyclic, annular, or gyrate arrangement and (2) keloid-like consistency. In the true cases the surface lacks scales, crusts, and vesicles. The color varies from pink to ivory-yellow, and the centers of the lesions in some cases become slightly pigmented. The palpating finger feels a rubber-like resistance. The pinkish elevated border slopes abruptly toward the healthy skin, while the decline inside the lesion is gradual.

I included erythema exudativum multiforme in our table only to recall the various names under which this clinical entity was known before Hebra [25] brought order into a confusing and almost chaotic terminology. All other erythemas described up to 1928 and included in the table showed—where illustrations could be located—configurations which clearly demonstrated that they were the result of confluence of larger annular or reniform lesions, such as are seen in dermatophytosis, tuberculosis of the skin, and serpiginous syphiloderm. I could not find a dermatological picture such as mine suggesting the graining of a wooden panel. The keloid-like consistency of erythema annulare centrifugum was absent. The palpating finger could feel almost no swelling of the skin. The histologic picture is compatible with that of Darier,[18] yet the same microscopic characteristics can be found also in other dermatoses and is by no means pathognomonic.

There is almost nothing known about the causation of the rare erythemas. Only in erythema chronicum migrans of Afzelius [26] and Lipschütz [27] has the bite of a wood tick been observed in a fair number of cases. Yet even here it is uncertain whether the eruption is due to a toxin introduced by the bite of an infectious agent.

Perhaps I should hesitate to add another name to the imposing array of dermatological terms. I admit, of course, that first and single observations often have to be supplemented later and by other investigators, but I have always looked with disdain upon efforts to force widely differing atypical cases into one diagnostic category or another. Erythema exudativum multiforme and erythema annulare centrifugum are terms used very loosely. Many cases are carried under these headings which bear very little resemblance to the concept of the originators of these terms and serious later students of these conditions.

If one wanted to be radical, one could do away with all of them and be satisfied with the diagnosis of erythema toxicum, but this, too, would serve no useful purpose. Until more is known about the normal variations of these erythemas and their etiology case reports and new terms are justified until further experience and perhaps new avenues of research permit simplification of their classification and terminology.

25. Hebra, F.: Diseases of Skin, translated and edited by C. H. Fagge, London, New Sydenham Society, 1866-68, Vol. 1, p. 285; cited by Corlett, W. T.: Erythema Exudativum Multiforme, Its Present Significance: With a Report of a Case of Erythema Circinatum Bullosum et Haemorrhagicum, Following a Gun Shot Wound, Apparently Due to Streptococcus Infection and Terminating Fatally, J. Cutan. Dis. **26**:7-14, 1908; cited by Tachau, P., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Springer-Verlag, 1928, Vol. 6, Pt. 2, p. 584.

26. Afzelius, A.: Erythema chronicum migrans, Acta dermato-venereol. **2**:120-125, 1921; abstracted, Zentralbl. Haut- u. Geschlechtskr. **4**:28, 1922.

27. Lipschütz, B.: Über eine seltene Erythemform (Erythema chronicum migrans), Arch. Dermat. u. Syph. **118**:349-356, 1914; ibid. **143**:365-374, 1923.

I believe the clinical picture described here is of sufficient distinction to be classified as a new entity, erythema gyratum repens. It is considered to be caused by endogenous allergy, in my case a carcinotoxin. It began about the time a carcinomatous neoplasm was formed in the patient's breast; it grew in intensity parallel to the parent tumor and disappeared when the tumor was removed and its products had been eliminated. It remains to be seen whether toxic agents (noxae) other than carcinoma may produce the same clinical picture.

SUMMARY

An unusual type of scaly erythema of about eight months' duration is described. The configuration resembled somewhat the graining of a wooden panel (cypress burl). The entire body with the exception of hands and feet was involved. In the late stages an eczematoid eruption appeared on the head. The eruption cleared up within a few weeks after removal of a cancer of the breast and the metastatic lymph nodes.

A relationship between the carcinoma and the dermatosis is assumed.

This is probably the only case on record in which a patient with skin manifestations apparently due to carcinoma of an internal organ survived four years.

ABSTRACT OF DISCUSSION

DR. FRANCIS A. ELLIS, Baltimore: Dr. Gammel has reviewed the literature concerning the occurrence of cutaneous eruptions associated with internal cancers. He suggested that when the eruption disappears after removal of the cancer one may assume that there is a relationship between the eruption and the cancer, but there was not a uniform type of cutaneous eruption associated with the malignant neoplasm. He found nine cases of this type in the literature and reported another one.

Dr. Gammel has speculated on what caused the cutaneous eruption and suggests a toxic material from the cancer as a possible agent. This theory seems somewhat acceptable, especially when one considers the time relationship between the disappearance of the eruption and the removal of the cancer in the cases reviewed.

Secondly he has reviewed the literature on the persistent erythemas. His time was somewhat short for presentation of this part, but he covered it in more detail in his paper. We consider erythema annulare centrifugum the same as erythema gyratum perstans of Colcott Fox and Wende's erythema figuratum perstans. Although Darier stressed that erythema annulare centrifugum should never show any evidence of scaling, exudation, vesiculation, or crusting, many cases that are otherwise typical may show a moderate amount of these changes.

Dr. Gammel stressed that in erythema annulare centrifugum there is an infiltrated border with a slightly pigmented center. I think that one of the most important clinical features is the fact that the active lesion is palpable and, therefore, infiltrated. In correlation with this is the fact that histologically there is usually a fairly definite pathologic picture in which the epidermis is essentially normal, but there is a dense perivascular infiltrate of lymphocytes and this infiltrate varies in intensity and depth with the amount of clinical infiltration.

In Dr. Gammel's case there was clinically very little or essentially no clinical infiltration. It was a macular eruption, and, therefore, of course, the infiltrate seen histologically was slight. Dr. Gammel wished to introduce a new term, erythema gyratum repens. After reviewing the histologic sections of Dr. Gammel's case I was unable to make a diagnosis of erythema annulare centrifugum. If erythema annulare centrifugum can be macular, then Dr. Gammel's patient may have had this disease. Only when the etiology of these annular erythemas is better known can one speak with finality on these points.

It is noted that the clinical picture of Dr. Gammel's patient was certainly different from that seen in the usual case of erythema annulare centrifugum. The need is for more knowledge of etiology rather than for more terms. I enjoyed the paper very much with its scholarly presentation.

DR. MAURICE J. COSTELLO, New York: I enjoyed Dr. Gammel's paper and appreciate the message it contains. During the past year I have seen three cases of dermatomyositis associated with carcinoma. Two of the patients had adenocarcinoma of the ovary. In one case the diagnosis was suspected before the patient's demise and, on postmortem examination extensive metastases were observed. In the second case the diagnosis of adenocarcinoma of the ovary was anticipated because of the experience in the first case. A grapefruit-sized mass was palpated in the left lower quadrant of the abdomen. When the tumor was excised there followed almost complete involution of the dermatomyositis. Recently, eight months after the surgical removal of the tumor, there is a beginning recurrence of the dermatomyositis. This may indicate recurrence of the tumor or metastases. In the third case, occurring in a Chinese man, a neoplasm was thought to be present. Six weeks after he first sought help for his dermatomyositis, a lump appeared in the left cervical region; this proved to be a lymphoepithelioma, a tumor not uncommon in Chinese males. There were three other cases of coexistence of ovarian carcinoma and dermatomyositis. The diagnoses were made by dermatologists in the New York City area in the past six months.

An article appeared in the *Annals of Internal Medicine* about a year ago in which the author reported the association of dermatomyositis and carcinoma of the viscera, six of the neoplasms, the greatest number, existing as adenocarcinoma of the ovary. In my own case, it was reasonable to conclude from the history and the time of the occurrence of the symptoms of the two conditions that the tumor preceded somewhat the dermatomyositis. Was the tumor the initiating cause of dermatomyositis in these cases? Was the tumor only one of the causes? Did the occurrence of the two conditions in the same patient at the same time indicate mere coincidence? Pruritic bullous eruptions not following the morphologic pattern of dermatitis herpetiformis (Duhring) should also suggest the possibility of coexisting internal neoplasm. Referring more directly to Dr. Gammel's paper, I have seen erythema multiforme associated with visceral neoplasms. It is not an uncommon experience to see bullous erythema multiforme and pruritic papular eruptions follow intensive radiation therapy of abdominal tumors.

DR. STEPHEN ROTHMAN, Chicago: The interesting problem of cutaneous manifestations due to internal cancers was reviewed by me in 1925 (*Arch. f. Dermat. & Syph.* **149**:99, 1925) and again, in collaboration with Becker and Kahn, in 1942 (ARCH. DERMAT. & SYPH. **45**:1069, 1942). Generalized pruritus due to gastrointestinal cancers was first reported by Kuettner. Several case reports on toxic eruptions subsiding after removal of the malignant tumor and relapsing with the recurrence of the neoplasm followed. The most interesting feature of these eruptions has been the gradual transformation of purely inflammatory lesions into true metastases. I am inclined to assume that for a while the skin is able to decompose single metastasizing malignant cells, with inflammatory reactions resulting. Later, with more massive invasion of the skin by tumor cells, development of metastases can no more be halted. So-called toxic eruptions in lymphoblastomas may have a similar mechanism.

DR. ARTHUR W. STILLIANS, Chicago: I was privileged to watch for a short time a patient who for some years had had indications of abdominal trouble. The distress was relieved by x-rays, but it recurred, and finally an exploratory operation was done at the hospital. Multiple metastases of carcinoma were found in her abdomen. Shortly after that operation erythema annulare centrifugum developed on both thighs. This eruption persisted until her death, a few months later.

I am more inclined to blame the eruption on the failure of the operation, to relieve her ascites and consequent distress. This could have caused enough mental distress to bring about the skin condition. The relation of erythema annulare centrifugum to urticaria and dermatitis herpetiformis seems to be fairly well established.

DR. HERMAN V. ALLINGTON, Oakland, Calif.: I should like to record the case of a 61-year-old white man who died of a rapidly progressive dermatomyositis. At the autopsy an unexpected early bronchogenic carcinoma was found. Incidentally, this patient had a history of peptic ulcer some 20 years previously but it had long since been quiescent. His death was hastened by a flare-up and perforation of this ulcer, while he was being given adrenocorticotropic hormone.

DR. NORMAN N. EPSTEIN, San Francisco: I should like to report the case of a white man, aged 74, who came to me with a bullous eruption which was indistinguishable from the clinical picture of pemphigus vulgaris. The bullae continued to develop over a period of several months.

A carcinoma of the sigmoid part of the colon was discovered. The lesion was removed, and the pemphigus-like eruption disappeared. This man is still alive some five years later. He has had an occasional bulla since then. The carcinoma and the bullous eruption appeared to me to be related.

DR. JOHN A. GAMMEL: I want to thank Dr. Ellis and the other discussers for the interest shown in this paper. Since Dr. Epstein's patient is still alive after five years, he has beaten the record I had hoped to establish.

I agree with Dr. Ellis that we should be more interested in a new etiology than in new terminology of the rare erythemas. I believe I have contributed something to the etiology too. In studying the erythemas I found that in all, with the exception of possibly Hebra's and Arning's cases, the lesions begin as papules or plaques which spread peripherally and result in configurations similar to those seen in superficial mycoses.

As there is none among the erythemas hitherto described suggesting the graining of wood, I felt justified in creating a new entity. I admit that I am not happy about the choice of the term. I have discussed the question of terminology with philologists and botanists of two continents without coming to an entirely satisfactory conclusion. Neither the classic nor the scholastic Latin or Greek has a word for "grain" of wood. The French *madrure* goes back to an old Germanic root.

Originally I presented the case as erythema gyratum migrans before the Cleveland Dermatological Society (ARCH. DERMAT. & SYPH. **61**:526 [March] 1950). I believe erythema gyratum repens is more appropriate. The eruption does not "migrate" from one place to another but "crawls" constantly in the areas involved, like ants on an anthill.

INTRACUTANEOUS HYALURONIDASE ACTION IN NORMAL AND ROENTGEN-IRRADIATED RABBITS

Histological Study

HUGH B. PRAYTOR, M.D.
MONTGOMERY, ALA.

THE PURPOSE of this investigation is to study histologically the effect of hyaluronidase on the diffusion of India ink in normal and in roentgen-irradiated cutaneous tissue of the rabbit.

The average spread of India ink with hyaluronidase was demonstrated to be 3.9 times greater than that of the India ink controls in a previous investigation of the biological effect of roentgen therapy.[1] It was further demonstrated that this spread was not significantly altered by roentgen irradiation administered prior to the injection of India ink and hyaluronidase. Those injection sites were removed for histologic examination and provided the material for this investigation. A microscopic study of the injected tissue was essential to determine whether or not histologic changes existed that were not grossly reflected in the spreading action of India ink.

In 1928 Duran-Reynals initiated an investigation of the spreading factors by demonstrating the enhancing effect of testicular extract on the dissemination of vaccinal infection.[2] The enhancing or spreading factors were subsequently demonstrated in invasive bacteria[3] and in poisonous insects and snake venoms.[4] Chain and Duthie[5] in 1940 concluded that the spreading factor and hyaluronidase were identical. This enzyme decreases the viscosity of hyaluronic acid in connective tissue ground substance and thereby increases tissue permeability.

MATERIAL AND METHOD OF STUDY

Twenty-four New Zealand albino rabbits varying from 12 to 20 weeks of age and weighing from 1.34 to 3.6 kg. were divided into four equal groups. Each group consisted of an equal number of male and female rabbits except group IV, which consisted of five females and one male. All rabbits were of the same stock.

From the Department of Dermatology and Syphilology (Dr. Ray O. Noojin, Professor and Chairman), Medical College of Alabama, Birmingham, Ala.

1. Noojin, R. O., and Praytor, H. B.: Hyaluronidase Action in Normal and in Roentgen-Irradiated Rabbit Skin, A. M. A. Arch. Dermat. & Syph. **63**:191-199 (Feb.) 1951.

2. Duran-Reynals, F.: Exaltation de l'activité du virus vaccinal par les extraits de certains organes, Compt. rend. Soc. biol. **99**:6-7 (June) 1928.

3. Duran-Reynals, F.: Studies on a Certain Spreading Factor Existing in Bacteria and Its Significance for Bacterial Invasiveness, J. Exper. Med. **58**:161-181 (Aug.) 1933.

4. Duran-Reynals, F.: A Spreading Factor in Certain Snake Venoms and Its Relation to Their Mode of Action, J. Exper. Med. **69**:69-81 (Jan.) 1939.

5. Chain, E., and Duthie, E. S.: Identity of Hyaluronidase and Spreading Factor, Brit. J. Exper. Path. **21**:324-338 (Dec.) 1940.

Preparation of the animals for irradiation or for injection was begun by clipping the fur from the lateral trunk. Barium sulfide was then applied to the clipped area as a depilatory.[6] After three to five minutes this was washed off with running tap water.

All rabbits except the nonirradiated control group (group I) were irradiated with a single exposure of roentgen rays to the left lateral trunk between the anterior and posterior extremities. The remainder of each animal had been previously screened with 0.1 mm. of lead. The irradiation was produced by a Westinghouse "dermadex" shock-proof x-ray machine with valve-tube rectification. The following formula was used: 85 kv., 5 ma., no added filtration, a skin-focus distance of 20 cm. and a half-value layer of 0.7 mm. of aluminum. The dosage administered to each animal was 400 r to those in group II, 800 r to those in group III, and 1,600 r to those in group IV. The right lateral trunk was not irradiated.

A hyaluronidase and India ink mixture and diluted India ink were injected intracutaneously on each side of all animals. The India ink-hyaluronidase mixture was composed of 500 turbidity-reducing units of hyaluronidase [7] in 0.25 ml. of isotonic sodium chloride solution plus 0.25 ml. of a 1:2 dilution of Higgins India ink in isotonic saline. The diluted India ink consisted of 0.25 ml. of isotonic saline plus 0.25 ml. of a 1:2 dilution of Higgins India ink in isotonic saline.

The intracutaneous injections were administered in two separate series. A single series of injections consisted of injecting hyaluronidase-India ink mixture into one site and diluted India ink into another site on each side of all animals. The injection sites were separated as far as possible to avoid overlapping of the India ink spread. In the control group the two series of injections were separated by an interval of five weeks. The first series of injections was administered to the irradiated animals one week after irradiation. The second series was given at the end of five weeks to the rabbits irradiated with 400 r (group II) and 800 r (group III). This was six weeks after irradiation. Since three out of six of the rabbits irradiated with 1,600 r died within three weeks following irradiation, it was necessary to administer the second series of injections to the three remaining rabbits four weeks after irradiation.

The rabbits were killed one week after the second series of injections. The animals were killed by injecting 2 to 3 ml. of ether into the marginal vein of the ear. The eight injection sites on each rabbit were excised and immediately fixed in 10% aqueous formalin solution. The tissue removed for histologic examination included normal cutaneous tissue beyond the spread of India ink.

Preparation of the tissue for examination was begun by cutting each specimen into a rectangular form. The tissue was then bisected through the site of injection. Specimens too large to be mounted on glass slides were also transected. The tissue was imbedded in paraffin and sections 6 to 8 μ thick were cut with a rotary microtome. These sections were stained in Harris' alum hematoxylin and in 5% eosin Y in 50% alcohol.

CONTROL GROUP

At the beginning of the experiment those rabbits which were not irradiated received intracutaneous injections of the hyaluronidase-India ink mixture and the diluted India ink on each side. The injections were repeated at the end of five weeks. The tissue used for histologic examination was removed one week later. The cutaneous histology of the nonirradiated rabbits and the intracutaneous diffusion of India ink in these animals were a base line with which the roentgen-irradiated tissue could be compared.

6. Carmichael, E. B.: A Convenient Preparation for the Removal of Hair, Science **75**:136-137 (Jan.) 1932.

7. The hyaluronidase was supplied by the Ortho Research Foundation, Raritan, N. J. It was prepared from bull testes. A turbidity-reducing unit is that amount of hyaluronidase which will just reduce the turbidity caused by 0.2 mg. of hyaluronic acid under appropriate conditions to that produced by 0.1 mg.

The stratified squamous epithelium of the nonirradiated control group varied from three to five cells in depth. This was covered by a stratum corneum which in some tissue sections equaled in thickness the remainder of the epidermis. Deep to this layer the stratum granulosum had a depth of one to two spindle cells, which contained dark nuclei and basophilic intracytoplasmic granules. A stratum lucidum was not present. The prickle cell layer was formed by a layer of one to two large polyhedral cells. Deep to this was a single row of cuboidal or basal cells. In some areas a well defined basal layer was not observed. The nuclear membrane and chromatin granules were more prominent in the basal cells than in the polyhedral cells.

The corium consisted primarily of a fibrous tissue framework supporting numerous hair follicles. Few capillaries were observed. The superficial corium began as a thin zone of closely interwoven fine acidophilic fibers deep to the basal layer of the epidermis. Most of these fibers ran in bundles parallel to the epidermis. Similar fibers were observed interweaving between this layer and the coarser collagen bundles below. The hair follicles in the superficial corium consisted of numerous groups of small follicles which were usually related to a single large follicle. Arrectores pilorum muscles coursed obliquely upward from the large follicles to the epidermis. One to three separate rows of groups of hair follicles were found at different levels in the corium of a single section. This was probably due to the large number of hairs and the acute angle they made with the cutaneous surface. Hair follicle bulbs were found in the deep corium. The hair follicles were more closely grouped as they approached the cutaneous surface, where several follicles communicated with a single opening in the epidermis. Fine interlacing fibers surrounded the hair follicles. In the subcutaneous tissue and at its junction with the lower corium deep to the hair follicle bulbs most of the narrow connective tissue fibers ran in bundles parallel to the epidermis. In the superficial corium, small sebaceous glands were related to some of the hair follicles. Sweat glands were not present.

The most prominent histological difference between the cutaneous tissue of the rabbit and the human is the tremendous number of small hair follicles in the rabbit and the relationship of the connective tissue to these follicles. In sections cut at 90 degrees to the plane of the hair follicles most of the connective tissue ran in bundles parallel to the rows of groups of hair follicles (Fig. 1). In sections cut parallel to the plane of the hair follicles most of the connective tissue ran in bundles parallel to the plane of the individual follicles (Fig. 3). The oblique arrangement of parallel rows of groups of hair follicles separated by connective tissue bundles running in planes parallel to these follicles gives the cutaneous tissue of the rabbit a laminated appearance.

In the subcutaneous layer loosely-woven narrow connective tissue fibers formed a network around an occasional arteriole or venule and interlaced with fibers of the deep corium. Deep to the subcutaneous connective tissue was a continuous layer of skeletal muscle, the panniculus carnosus.

There were certain features of the diffusion of India ink that were characteristic of all sections. The greatest concentration of free India ink was found in the site of injection. This ink extended from the basal cell layer of the epidermis through the corium and subcutaneous tissue to the outer border of the skeletal muscle layer. In all sections, macrophages were found beyond the dense collections of India ink.

The peripheral diffusion of India ink from the injection sites was least in the superficial corium, greater in the deep corium, and greatest in the subcutaneous tissue of all sections (Fig. 1). The great abundance of India ink in the center of the injection sites of some tissue sections obscured a regular pattern of India ink distribution. The connective tissue stained pale in the center of the injected tissue and stained brighter as the concentration of India ink diminished. Free India ink did not extend into the skeletal muscle layer but a few macrophages were present in this region.

An important observation in all sections was the relationship of India ink to the cutaneous structures. The laminated appearance of the cutaneous tissue due to the

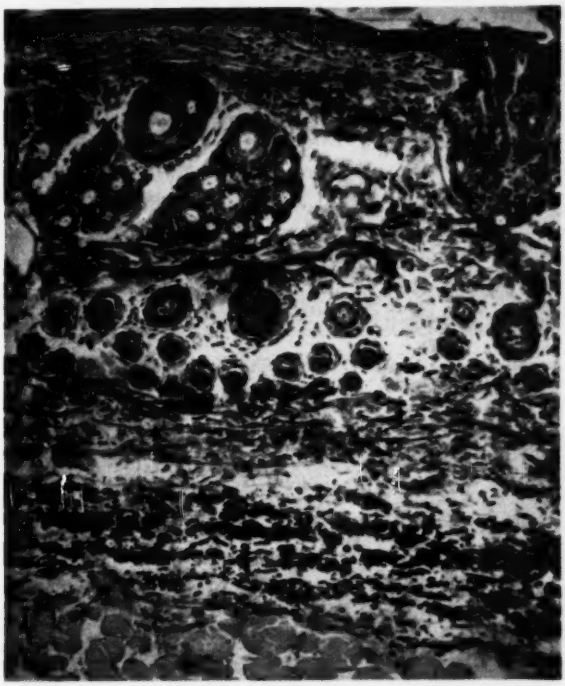


Fig. 1.—Cutaneous tissue showing India ink in the loose connective tissue above the cutaneous skeletal muscle layer of a rabbit in the control group one week after the injection of hyaluronidase and India ink; × 105.

arrangement of the hair follicles and connective tissue was simulated by the distribution of India ink between those structures (Figs. 2 and 3). In the subcutaneous layer the longest axis of most of the individual collections of India ink was parallel to the epidermis and to the skeletal muscle layer (Fig. 1).

The tissue injected with diluted India ink one week before biopsy differed only slightly from that injected six weeks prior to biopsy. In the tissue injected one week before biopsy the majority of the India ink collections were smaller and a regular pattern of India ink distribution was less marked. The fine lines of India ink appearing inside collagen bundles separated the fibrils. Dilated capillaries were more

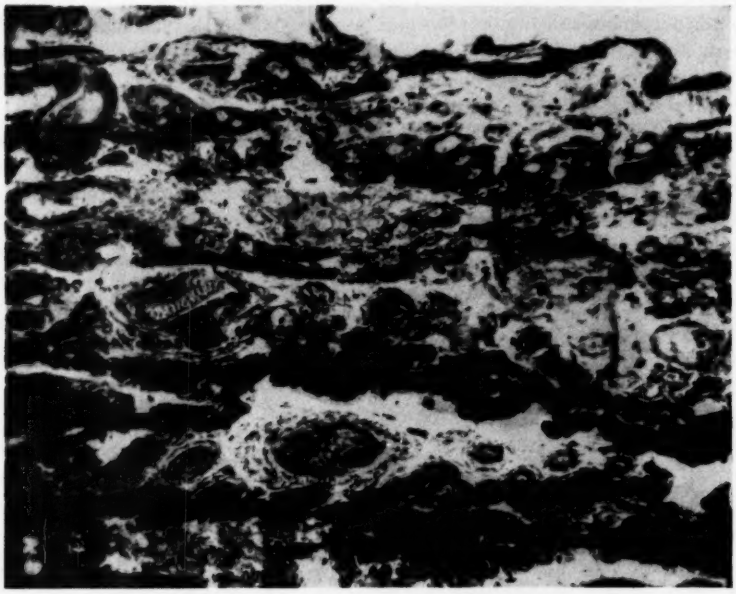


Fig. 2.—India ink parallel to rows of hair follicles in a rabbit of the control group six weeks after the intravenous injection of India ink; × 280.

Fig. 3.—India ink parallel to the longitudinal axis of individual hair follicles in a rabbit of the control group six weeks after the intracutaneous injection of India ink; × 255.

numerous. In the deep corium and subcutaneous tissue small arterioles with intact endothelium, thickened walls, and narrowed lumens were surrounded by an inflammatory infiltrate of eosinophilic polymorphonuclear leucocytes and mononuclear leucocytes. A dense perifollicular inflammation occurred in some sections but did not extend beyond the distribution of the India ink. Several small abscesses were present in the injected areas.

In sections from tissue injected six weeks previously with diluted India ink the inflammatory reaction in the area containing India ink consisted of occasional mononuclear leucocytes and numerous macrophages. The rare groups of fine intercellular India ink particles in the basal cell area were not observed in the same focal plane as the nuclei of those cells.

The hyaluronidase-India-ink-injected tissue differed from the corresponding India ink controls. In the hyaluronidase-India-ink-injected tissue the ink collections were smaller and more diffusely scattered. A wider distribution of ink occurred just deep to the basal layer of the epidermis in most of the sections. The longest dimension of these collections of ink was approximately parallel to the epidermis. This pattern was occasionally interrupted by hair follicles. Scattered chronic inflammation appeared occasionally in the superficial corium and was associated with connective tissue proliferation in a few sections. The maximum spread of India ink in the subcutaneous tissue above the skeletal muscle layer was similar to that in the control injections.

ROENTGEN-IRRADIATED GROUPS

The roentgen-irradiated rabbits received irradiation to the left side only, whereas both sides were injected intracutaneously with the hyaluronidase-India ink mixture and the diluted India ink. The first series of injections was made one week after irradiation, and the second series was administered at the end of six weeks following irradiation to all except those rabbits irradiated with 1,600 r. A 50% mortality in group IV within three weeks following irradiation with 1,600 r made it necessary for the second series of injections to be administered to the three remaining rabbits four weeks following irradiation. The tissue for histologic study was removed one week after the second series of injections.

The rabbits irradiated with 400 r (group II) and 800 r (group III) showed no differences histologically and consequently will be discussed together. Cutaneous evidence of irradiation damage could not be demonstrated in these animals. The pattern of India ink diffusion in the bilateral sites injected with hyaluronidase-India ink mixture and also those sites injected with diluted India ink did not differ in the irradiated and nonirradiated sides of each animal. The animals in the nonirradiated control group showed a similar pattern of intracutaneous India ink diffusion.

Radiodermatitis was present on the irradiated side of all rabbits irradiated with 1,600 r (Fig. 4). The evidence of irradiation damage was less severe in the three rabbits that died within three weeks following irradiation than in the animals killed five weeks after irradiation. The intracutaneous diffusion of India ink in these animals did not differ from that of the control group.

In the cutaneous tissue irradiated five weeks previously with 1,600 r, atrophy and ulceration predominated, with an occasional area of hyperplasia. The pale-stained epidermis was composed of cells having a greater variation of size and contour than observed in the control animals. Giant epithelial cells with prominent

nucleoli were observed. Occasionally large multinucleated epithelial cells were seen. Many of the basal cell nuclei were pyknotic. Scattered areas of hyaline degeneration occurred in the prickle cell layer. The edematous connective tissue of the superficial corium contained many dilated capillaries and a diffuse subacute inflammatory infiltration. The connective tissue in the superficial corium stained lighter than in the deep corium.

Although reduced in number, the dermal appendages were not completely destroyed by irradiation with 1,600 r. Pale staining and vacuolation were observed in the arrectores pilorum muscles. Hair follicle bulbs were absent from the irradiated tissue, but remnants of hair follicles were observed in the superficial corium of all six animals. Sebaceous cells were present in the irradiated tissue in four of

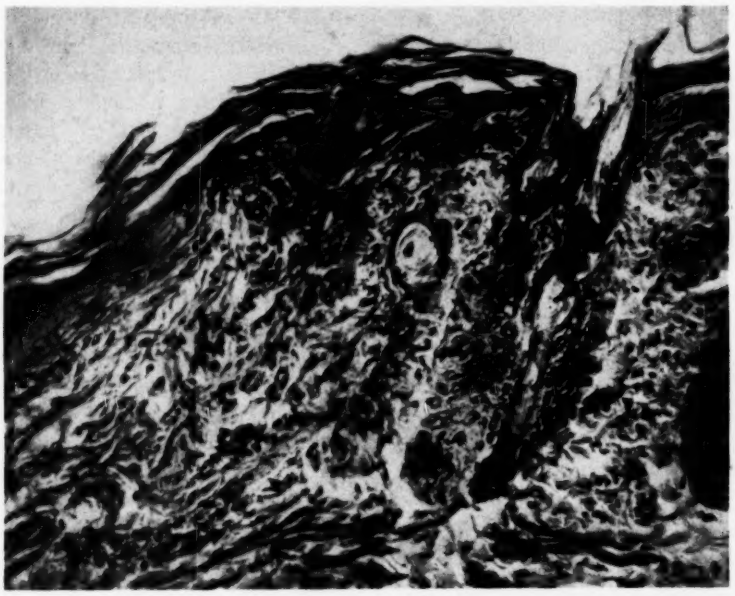


Fig. 4.—Radiodermatitis showing remnant of a sebaceous gland three weeks after irradiation with 1,600 r; × 240.

six rabbits (Fig. 4). The two animals not showing sebaceous cells died within three weeks following irradiation.

Vascular evidence of irradiation damage was observed in the irradiated tissue of all six rabbits irradiated with 1,600 r (Fig. 5). These changes varied from thickening of the vessel walls with endothelial proliferation to obliterative endarteritis. The greatest degree of vascular damage occurred in areas of inflammatory infiltration. Four of six rabbits showed vascular damage bilaterally. Two of the three rabbits that died within three weeks following irradiation showed vascular damage only on the irradiated side.

Free India ink was observed in the atrophic subcutaneous skeletal muscle layer in five of six rabbits irradiated with 1,600 r. This finding was not confined to the

irradiated or the hyaluronidase-injected tissue. Free ink was not present in the skeletal muscle layer of rabbits irradiated with 400 r or 800 r or in the nonirradiated control group.

Histologic changes consistent with irradiation damage were also observed in the cutaneous tissue of the right lateral trunk in rabbits irradiated with 1,600 r to the left lateral trunk. These changes consisted of thickened arterioles with endothelial proliferation, dilated capillaries, edema and variable staining of the corium, small mononuclear leucocyte infiltration, and atrophy of the epidermis. Ulceration was not present.

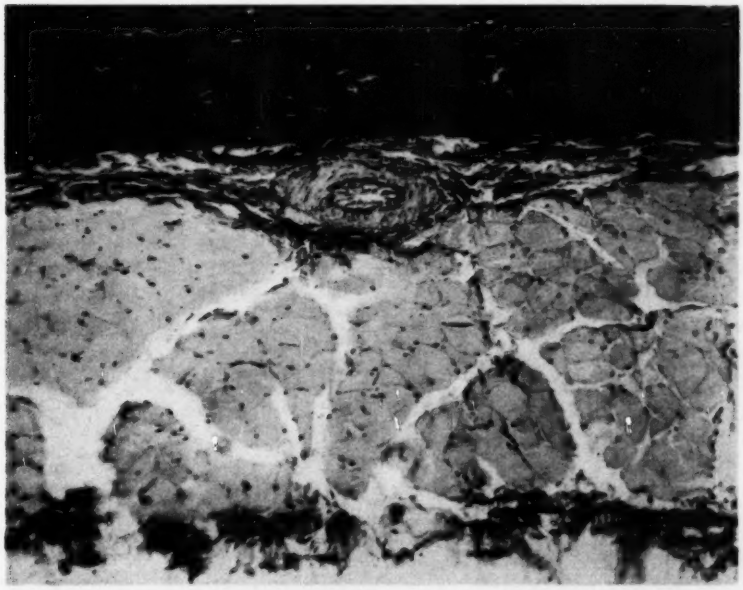


Fig. 5.—Endarteritis three weeks after irradiation with 1,600 r to the cutaneous tissue of a rabbit injected with India ink and hyaluronidase one week after irradiation; × 120.

India ink was present in the epidermal hyperplasia observed in six sections from different rabbits in the irradiated groups. This ink varied in size from very minute particles to collections the size of large epidermal cells. The amount of intracellular India ink did not vary with the dosage of roentgen irradiation or the presence or absence of hyaluronidase. The larger collections of ink appeared to have resulted from a fusion of smaller particles. Many of the smaller ink particles were observed in the same focal plane as the nuclei of the epidermal cells and were within the limits of the cytoplasm of those cells (Fig. 6). The structure and staining qualities of the cells containing India ink in the epidermis were consistent with epithelial cells rather than with macrophages that had migrated into the epidermis. Intercellular bridges were present between many of those cells. The minute India ink particles were in close apposition to the nuclei in most instances. In some cells the ink com-

pletely surrounded the nucleus. Some of the nuclei were distorted by the contour of larger India ink collections. In the keratin layer and in regions of parakeratosis the ink collections were similar in size and shape to those in the deeper epidermal layers. Occasionally an acidophilic band surrounded a collection of India ink about the size of an epidermal cell. India ink was observed in a nest of pale-staining stratified squamous cells deep within the cutis in the region of hair follicle bulbs of one section. As in the epidermis, the ink was in the same focal plane as the nuclei and located within the limits of the cytoplasm, but intercellular bridges could not be demonstrated. Evidence of either epidermal ulceration or microabscess formation was observed at the sites where India ink appeared in epithelial tissue.

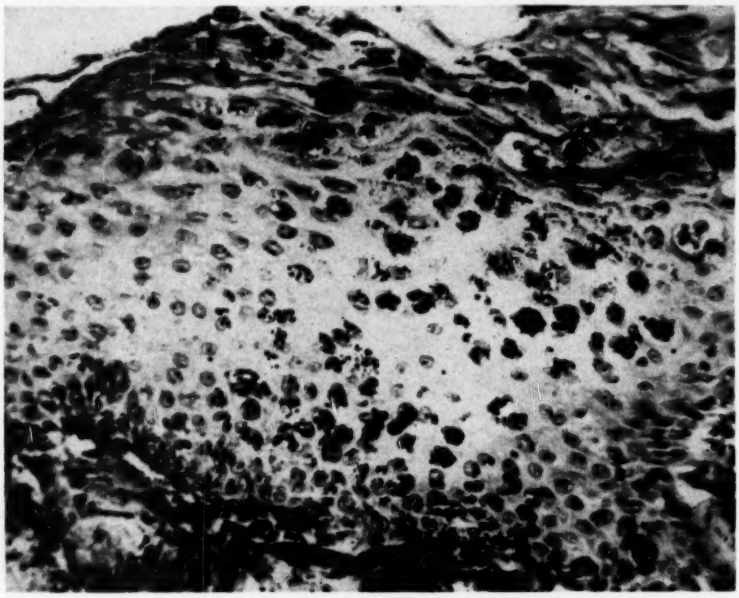


Fig. 6.—Hyperplasia of the epidermis, showing intracellular India ink in all layers of the epidermis seven weeks after irradiation with 800 r to the cutaneous tissue of a rabbit injected with hyaluronidase and India ink six weeks after irradiation; × 250.

*Occurrence of Intracellular India Ink in Epidermal Cells**

Rabbits	Sections Showing Intracellular India Ink, No.	Roentgen Dosage, r	Injection
Control group	0	0	India ink and India ink-hyaluronidase
Groups II, III and IV			
Nonirradiated side	1	400	India ink-hyaluronidase
Irradiated side	2	400	India ink
Irradiated side	1	800	India ink
Irradiated side	1	800	India ink-hyaluronidase
Irradiated side	1	1,600	India ink

* All tissue showing India ink in epidermal cells was removed for histologic examination one week after the second series of injections.

Five of the six sections showing India ink in epithelial cells were taken from irradiated tissue (Table 1). The section showing similar findings in tissue not irradiated came from the right side of a rabbit irradiated with 400 r to the left side. Serial sections were not made. This would be required of all injection sites in both the control and the irradiated animals to give an accurate analysis of the presence of India ink in epithelial cells in relationship to the previously administered roentgen irradiation. Since one section from tissue not irradiated showed India ink in epithelial cells, roentgen irradiation is probably not of primary significance. Hyaluronidase was present in only two of the six injections. The fact that all the tissue showing India ink in epithelial cells was removed one week after injection suggests that the initial trauma from the injection may have been a significant factor in the subsequent appearance of the ink in the epithelial cells.

COMMENT

The maximum spread of India ink in the subcutaneous tissue denotes that this particular pattern follows the route of minimum resistance in both the hyaluronidase-injected tissue and the tissue injected with diluted India ink. Hyaluronidase, by decreasing the viscosity of intercellular cement, would be expected to lower that resistance and enable a wider diffusion of India ink.

It is believed that observations made during this study establish the presence of India ink in epithelial cells. This suggests phagocytic activity, but further investigation will be necessary to evaluate accurately the manner in which India ink was introduced into the epithelial cells subsequent to roentgen irradiation. The presence of India ink collections of similar size throughout all layers of the epidermis signifies that epidermal proliferation may bring about a gradual removal of the ink from the epidermis. Trauma produced by the injection or excoriations produced by the animal may be factors contributing to the hyperplasia.

SUMMARY

The cutaneous histological features observed in 6 normal and 18 roentgen-irradiated rabbits following the intracutaneous injection of India ink and hyaluronidase are presented. The irradiated rabbits were divided into three equal groups and irradiated respectively with 400, 800, and 1,600 r at a single exposure to the left side. An India ink-hyaluronidase mixture and diluted India ink were injected intracutaneously into each side of all rabbits. The cutaneous histology of the rabbit is reviewed.

CONCLUSIONS

1. The ink diffusion in the hyaluronidase-India-ink-injected tissue differed from the tissue injected only with India ink by a more diffuse distribution of smaller particles of ink.

2. The intracutaneous diffusion of India ink in the irradiated tissue resembled that of the nonirradiated opposite side in each irradiated rabbit.

3. The intracutaneous diffusion of India ink in the irradiated rabbits was similar to that of the nonirradiated control group.

4. The greatest diffusion of India ink occurred in the subcutaneous tissue in all sections.

5. Histologic evidence of irradiation damage was observed in rabbits irradiated on only one side with 1,600 r. The rabbits irradiated with 400 and 800 r did not show histologic evidence of irradiation damage.

6. Histologic evidence indicating that previously administered roentgen irradiation in any way alters the intracutaneous diffusion of a hyaluronidase-India ink mixture could not be demonstrated.

7. The intracutaneous injection of hyaluronidase did not influence the severity of irradiation damage.

8. Intracellular India ink was observed in epithelial cells in areas of hyperplasia.

45 Adams Avenue.

Miss Mary Virginia Stallworth and Mrs. Virginia Gilbert gave technical aid in the preparation of the material for this study.

The photomicrographs were prepared by Mr. Joseph B. Beaird, Department of Pathology, Medical College of Alabama, Birmingham, Ala.

Clinical Notes, New Instruments and Techniques

ERYTHROPLASIA

Report of a Case with Cure

PERRY M. SACHS, M.D.
NEW YORK
AND
HANS FIELD, M.D.
BRONX, N. Y.

In 1948, in an article based on a series of 10 cases, Sachs and Sachs [1] stressed important facts pertaining to erythroplasia and noted unusual features of the disease. Furthermore, they challenged the concept that erythroplasia is a precancerous condition or a carcinoma and outlined a heretofore undescribed therapeutic regimen.

It is our intent to present a case of erythroplasia of unusual location that responded with apparent cure to the medication advised in the aforementioned report.

REPORT OF CASE

D. B., a white 62-year-old Jewish man, first consulted us on April 20, 1946. He complained of an oozing eruption of the scrotum (Fig. 1) and umbilical area of six months' duration. Accompanying this were pustular lesions on the index fingers and on the skin surrounding the left thumbnail.

At that time, the patient presented a silver-dollar-sized eczematous patch in the umbilical area. The scrotum, in the area contiguous with the ventral surface of the left side of the base of the penis, revealed a superficial erythematous, oozing, crusted, impetiginized plaque. The index fingers were edematous and erythematous and showed deep pustules in the subungual and periungual regions. The nails of these fingers were thinned, dystrophic, and friable. The terminal phalanx of the left thumb and the left thumbnail were similarly involved.

Between April, 1946, and April, 1949, the patient remained under supervision and was observed periodically. During this interval, various remedies were employed locally, including wet dressings, sulfadiazine (oral administration of which was also prescribed), and penicillin. In addition, fractional doses of roentgen rays had been administered. With the exception of the scrotal lesions, the affected areas responded adequately to treatment. The eruption of the fingers and nails proved to be recurrent but cleared upon removal of the involved nails. A mild folliculitis of the bearded region developed in January, 1949, and rapidly disappeared with topical medication and roentgen-ray therapy.

In April, 1949, the erythematous, oozing scrotal patch was the only lesion that still existed. This had been persistent and progressive, had never disappeared, and had been influenced slightly, if at all, by therapy. The clinical picture at this time suggested the diagnosis of erythroplasia, and a biopsy was performed, the findings of which corroborated this impression.

Microscopically (Fig. 2) the blood vessels throughout the upper cutis were dilated, and many were filled with blood elements. The upper cutis presented a mild interstitial edema and a moderately intense, diffuse cellular infiltration composed of small round cells, wandering connective tissue cells, plasma cells (Fig. 3), and numerous polymorphonuclear leucocytes, including eosinophiles. The epidermis was irregularly acanthotic and showed suggestively peg-shaped rete pegs. Some of the prickle cells appeared edematous, and there was a varying amount of intercellular edema (Fig. 4). Many polymorphonuclear leucocytes from the cutis had infiltrated

1. Sachs, W., and Sachs, P. M.: Erythroplasia of Queyrat, Arch. Dermat. & Syph. **58**:184-190, 1948.

Fig. 1.—Erythroplasia, showing exudative scrotal patch.

Fig. 2.—Erythroplasia, showing configuration of epidermis, dilated blood vessels, and inflammatory cells.

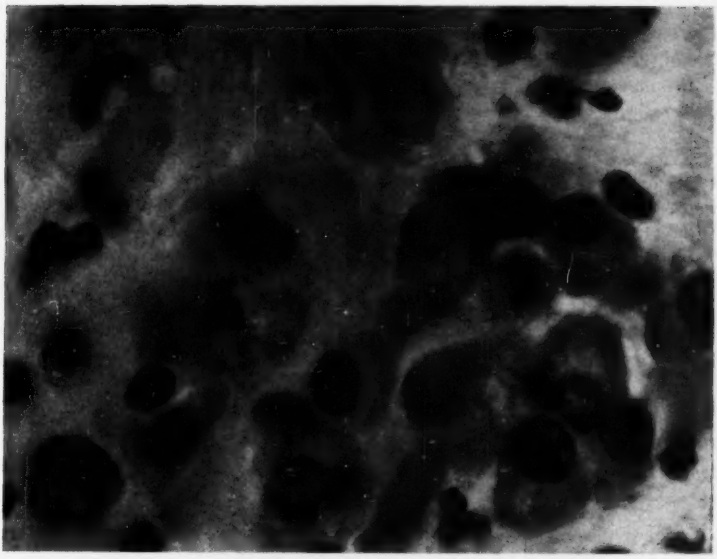


Fig. 3.—Erythroplasia, showing plasma cells at high magnification.

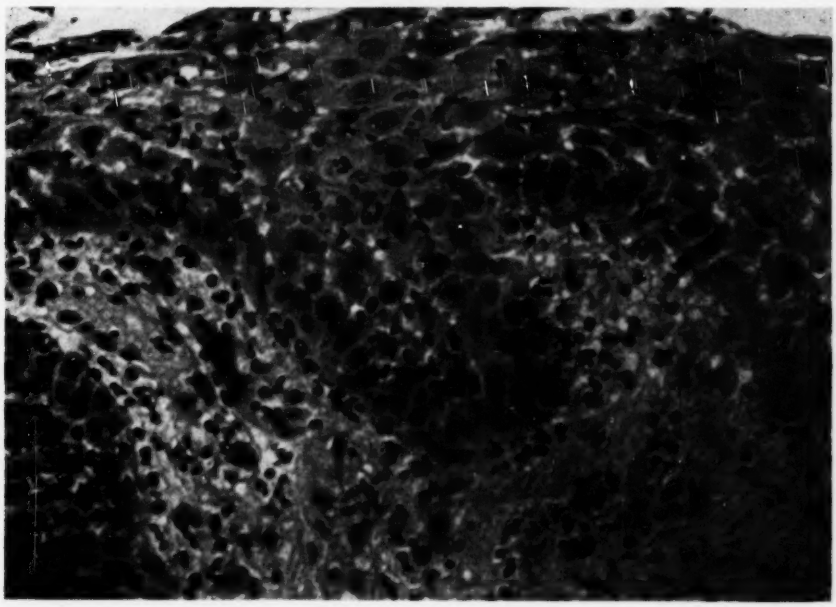


Fig. 4.—Erythroplasia, showing edema and inflammatory cells in the epidermis.

into the epidermis (exocytosis). The surface showed eroded areas, as well as collections of polymorphonuclear leucocytes and necrotic cells, indicative of crusting and impetiginization.

The Wassermann serologic reaction was negative. Examination of the urine revealed trace reactions for albumin and sugar. No fungi were found on examination of smears.

Once the diagnosis of erythroplasia was established, application of arsenic, as outlined by Sachs and Sachs, proved a successful mode of treatment.

COMMENT

It is difficult or impossible to state the exact relationship that the scrotal patch of erythroplasia bore to the other lesions demonstrable in this case. The latter group contained pustules and differed in clinical appearance. Moreover, they were of comparatively short duration and responded to an ordinary therapeutic regimen, in contrast to the indolent nature (three and one-half years' duration) and the more specific response to treatment of the scrotal lesion.

Most likely, the scrotal dermatosis was not related to and was independent of the other lesions. Nevertheless, we appreciate the possibility that the group of pustular eruptions was

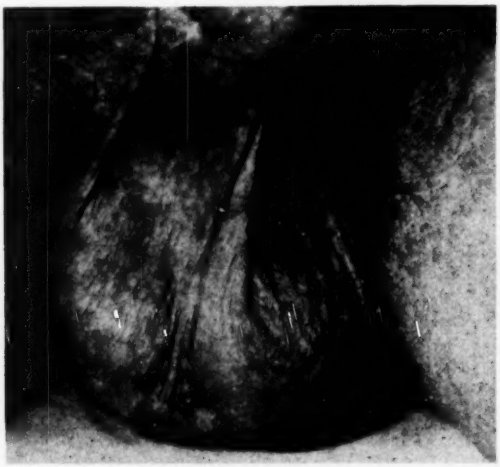


Fig. 5.—Erythroplasia, showing disappearance of the scrotal lesion following therapy.

secondary to the oozing, impetiginized erythroplasia patch. (The impetiginization in this instance was a result of the intertriginous location of the lesion between the scrotum and penis.) If this concept is correct, the eruption of the fingers, umbilicus, and bearded area of the face would be classified as a secondary pyogenic dermatosis.

This patient, as did those in the cited report, presented a lesion of long duration which did not respond to the usual indicated treatment. Furthermore, the scrotum as a site of involvement is in accord with a case described in the aforementioned article. In spite of the long duration, there was no clinical or microscopic evidence of neoplasm, a fact which further substantiates the conclusion that erythroplasia most probably is not a precancerous condition or a cancer. There was no evidence that syphilis played any role.

The treatment administered to this patient was that outlined by Sachs and Sachs and consisted of local application of an arsenic solution (neoarsphenamine, 0.3 gm., dissolved in 4 cc. of distilled water and 1 cc. of glycerin). The solution was painted on twice a week for 10 weeks. At the end of this time, the patient was apparently cured (Fig. 5), since the scrotal lesion had completely disappeared. In comparison with the other recorded cases, the therapeutic response of this patient to the medication was rapid. To date, we know that this patient has remained free of lesions for approximately two years.

SUMMARY

A case of erythroplasia involving the scrotum is presented. There was no evidence of neoplasm. The patient apparently was cured with local application of an arsenic solution, a form of treatment that was previously outlined for this dermatosis. Use of numerous other therapeutic agents was unsuccessful.

55 E. 86th St. (Dr. Sachs).

1686 Grand Concourse (Dr. Field).

ALOPECIA-AREATA-LIKE LESIONS DUE TO COLD-WAVE THIOGLYCOLATE PREPARATIONS

A. J. REICHES, M.D.
AND
WILLIAM PARKER, M.D.
ST. LOUIS

The public is now being overwhelmed by newspaper, radio, and television claims of the simplicity of so-called home permanent-wave treatments for both women and children. The incidence of untoward reactions from home and beauty-parlor cold-wave solutions is apparently increasing. We do feel that, even though the number of reactions is very small, use of these cold-wave preparations is not entirely devoid of complications.

Cold-wave permanents have been reported by Reiches and Lane [1] to cause areas of temporary alopecia of the scalp. The transitory baldness from thioglycolate cold-wave preparations at times has to be differentiated from alopecia areata of the scalp.

We are reporting two additional cases and a third in which temporary alopecia occurred for the second time. Two of the patients used home cold-wave preparations; the other was given the permanent wave at a beauty parlor. Both home and beauty-parlor cold-wave preparations are solutions of ammonium thioglycolate. Three cases are reported in detail.

REPORT OF CASES

CASE 1.—M. L., a 36-year-old woman, had been seen 15 months previously for loss of hair and an area of baldness 1⅜ in. (3.5 cm.) in diameter which appeared on the back of her scalp after a beauty-parlor cold-wave permanent. This defect had disappeared in four months. She reported that she had again had a cold-wave permanent one week ago and was perturbed because she could feel the hair breaking off on top of her scalp and feared that a bald spot was again developing.

On examination there was a small area of alopecia less than ½ in. (1.3 cm.) in diameter surrounded with broken-off hairs. This was close to the vertex area of the scalp. Hair began to regrow in about three or four weeks. Her general health has been good.

CASE 2.—T. W., a white woman aged 30, came in with complaint of loss of hair on the front of her scalp. She had applied a home permanent-wave solution four days previously.

On examination the hair in some areas on the front part of the scalp was broken off, and a few of these hairs came out with the hair bulbs on very light traction. One week later most of this easily-pulled-out hair had fallen, and an area of alopecia 1¾ by 2½ in. (4.5 by 6.4 cm.) appeared. Brunette hair began to grow within three weeks. The general health of the patient has been good.

CASE 3.—Z. S., a 19-year-old white girl, with chief complaint of areas of baldness on the scalp of about 10 days' duration, had applied a popular home permanent treatment three weeks prior to examination. The patient noticed that the ends of her hair began to break off the day following the home permanent. Within 7 to 10 days small bald areas were seen on various spots of her scalp.

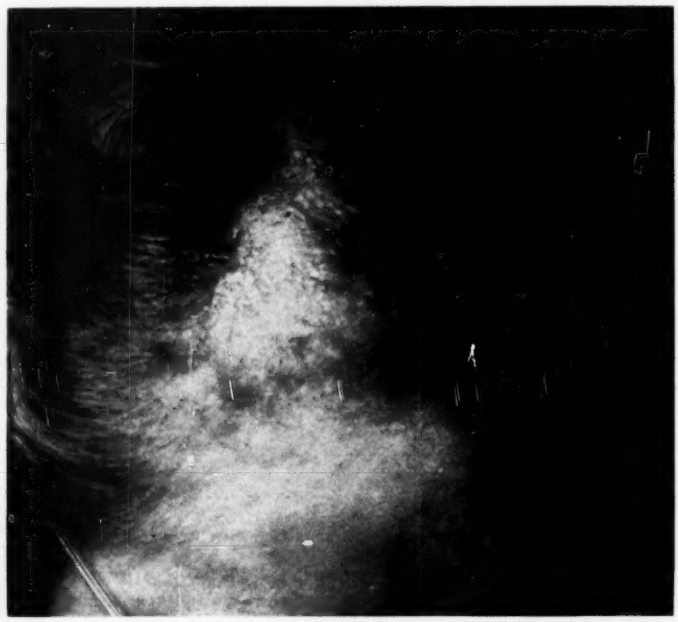
1. Reiches, A. J., and Lane, C. W.: Temporary Baldness Due to Cold Wave Thioglycolate Preparations, J. A. M. A. **144**:305 (Sept. 23) 1950.

On examination six circular areas devoid of hair varying from ½ to 1½ in. (1.3 to 3.8 cm.) in diameter were seen on the sides and back of the scalp. Several other areas showed sparse growth of hair. Brown hair began to regrow in about three weeks. Four months later there was complete regrowth of hair. The patient was in excellent health.

COMMENT

There are two types of cutaneous irritation from cold-wave thioglycolate preparations. One is a contact dermatitis and the other a transitory alopecia. Systemic symptoms [2] from ammonium thioglycolate have also been observed.

The patients with contact dermatitis from thioglycolate have been women and children who have had either home or beauty-parlor permanents. We have not seen many beauty-parlor operators who had a thioglycolate dermatitis from the cold-wave preparation, although Goldman, Mason, and McDaniel [3] believed that members of this occupational group, because of their frequent contact with thioglycolate solutions, exhibited cold-wave dermatitis oftener than did their patrons.



Frontal area of scalp showing bald patch.

The dermatitis is usually a primary irritation of the scalp, forehead, ears, and nuchal region, with pustular lesions about the hair roots. Cases have been reported in which there occurred an actual breakdown of old cutaneous scars.[2] Sataloff and Wilson [4] also have reported a case of perforation of the tympanic membrane due to thioglycolate cold-wave preparation.

2. Cotter, L. H.: Thioglycolic Acid Poisoning in Connection with "Cold Wave" Process, J. A. M. A. **131**:592 (June 15) 1946.

3. Goldman, L.; Mason, L., and McDaniel, W.: Permanent Wave Process: Clinical Report with Special Reference to Effect of Ammonium Thioglycolate on Skin, J. A. M. A. **137**:354 (May 22) 1948.

4. Sataloff, J., and Wilson, J.: Perforated Ear Drum Following Home Permanent Wave. J. A. M. A. **147**:1135 (Nov. 17) 1951.

In addition to the primary irritation, occasional systemic symptoms [2] may be the result of a hypersensitivity to ammonium thioglycolate. Among the reported symptoms are nausea, vomiting, jaundice, nocturia, and albuminuria, as well as possible anemia and leucopenia.

The temporary scalp alopecia, we feel, may be due to the irritating effect of the thioglycolate solution on the hair follicles in association with mechanical trauma from the too-tight application of hair curlers. This trauma may cause excess stress and strain on the hair follicles of the scalp and terminate in alopecia.

The round, oval, or irregular bald patches on the scalp resemble those of alopecia areata in that in both conditions these areas are white, soft, and smooth. In those cases in which transitory thioglycolate alopecia develops, broken-off hairs either fall or pull out with only slight traction. Many of these hairs, as Reiches and Lane [1] originally reported, come out with the intact hair bulb, similar to the "exclamation point" hairs of alopecia areata.

The diagnosis of cold-wave thioglycolate alopecia may be made from the history of recent use of ammonium thioglycolate, as well as on the basis of the early regrowth of hair (in our cases three to five weeks). The color of the early regrowth is the same as that of the hair on the rest of the scalp, in contrast to the early white hair regrowth in cases of alopecia areata.

SUMMARY

Two additional cases of temporary alopecia and another in which this same alopecia occurred for the second time after use of cold-wave thioglycolate preparations are reported.

Features differentiating the temporary alopecia following the use of cold-wave thioglycolate solutions from alopecia areata of the scalp are indicated.

AMALGAM TATTOO (LOCALIZED ARGYRIA)

CAPTAIN C. D. BELL (MC), U.S.N.
COMMANDER D. E. COOKSEY (DC), U.S.N.
AND
WALTER R. NICKEL, M.D.
SAN DIEGO, CALIF.

The accidental implantation of amalgam into the gingival and even the buccal mucosa is a condition well recognized clinically by dentists, but it may be unfamiliar to dermatologists. Recently we have had occasion to perform biopsies on such lesions, and we were impressed by the histopathologic changes. Search of both the medical and the dental literature failed to reveal a description of the characteristic histopathology, and, therefore, this report is submitted.

Silver amalgam is a dental filling material employed throughout the world for the restoration of carious teeth. It is composed of approximately 65% silver, alloyed with 25% tin, 6% copper, and 2% zinc. Bars of this alloy are reduced to a fine powder, washed in dilute hydrochloric acid, and packaged for the use of the practitioner. The dentist mixes this material with mercury, and, while the mixture is in the soft state, he introduces it into the prepared dental cavity and fabricates the restoration. Within 24 hours the amalgam achieves its full hardness and mechanically becomes a portion of the tooth.

Many times small amounts of the substance become implanted in the oral tissues; these range in size from gross radiopaque fragments, lodged in the alveolus or gingiva during a dental extraction, to small tattoos introduced by the nick of a contaminated dental burr or by the packing of fresh amalgam against an excoriation of an interdental papilla. Large particles are readily demonstrable on roentgenograms, as Prinz and Greenbaum [1] have stated, but minute

From the United States Naval Hospital, San Diego, Calif., Captain O. B. Morrison (MC), U. S. N., Commanding.

Chief, Dermatologic Service (Capt. Bell); Dental Service (Comdr. Cooksey), and Civilian Consultant, Dermatologic Service (Dr. Nickel).

The opinions or assertions contained herein are the private ones of the writers, and are not to be construed as official, or as reflecting the views of the Navy Department or the Naval Service at large.

1. Prinz, H., and Greenbaum, S.: Diseases of the Mouth and Their Treatment, Philadelphia, Lea & Febiger, 1935, p. 419.

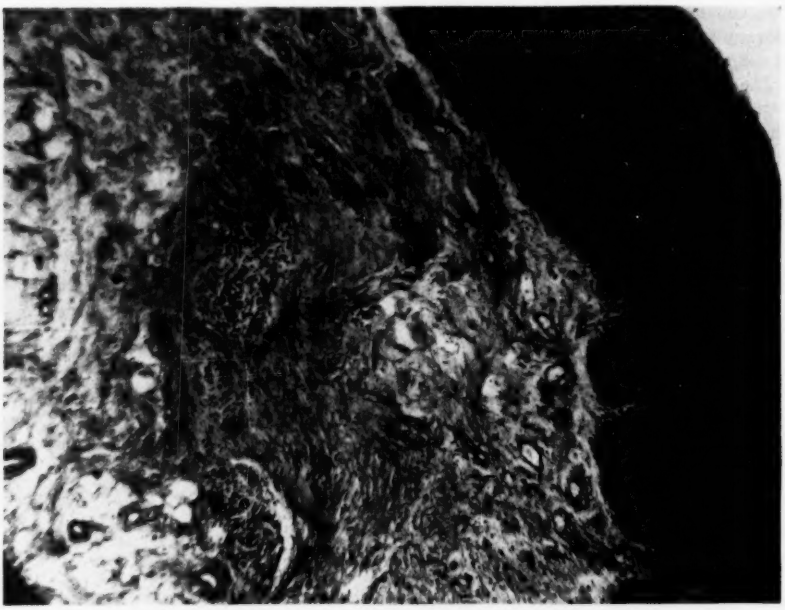


Fig. 1.—Low-power view; note resemblance to blue nevus.

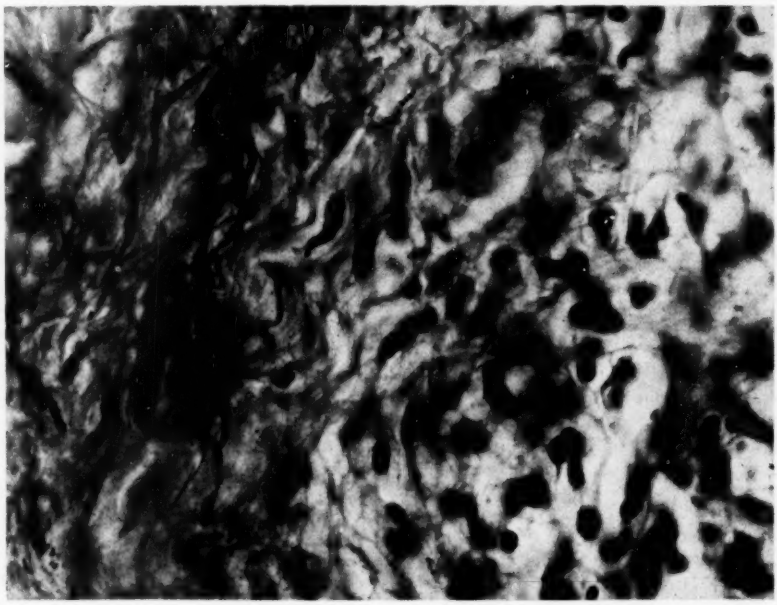


Fig. 2.—High-power view; note dark filamentous structures and globular masses.

quantities are not. Clinically, they appear as a grayish-blue macule in the oral mucous membrane, usually situated as noted above and most frequently seen in an edentulous area. They are flat, smooth, nontender, and noninflammatory, unless subjected to manipulation or stress, as when situated beneath a denture. They closely resemble a blue nevus and have been removed in some cases on suspicion of neoplasm.

The histopathologic picture is striking. Under low power with the usual hematoxylin and eosin stains, the epidermis is found to be unchanged. There are localized dark brown filamentous structures throughout the cutis and also larger, globular masses. These, together with a sparse sprinkling of histiocytes, at first glance give a strong impression of blue nevus (Jadassohn-Tièche). Under high power the filamentous pigmentation is composed of thread-like structures closely simulating hyphae and in some instances even mimicking the bead-like structure of the arthrospore. The larger globular masses appear only amorphous. No giant cells, inflammatory

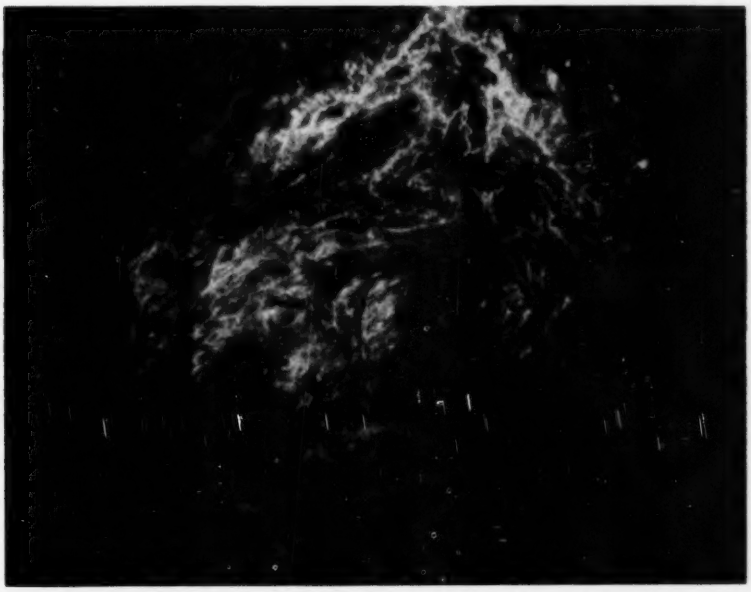


Fig. 3.—Dark-field illumination demonstrating luminescent filaments.

infiltrates, or other tissue reactions have been seen. Under dark-field illumination the whole area of the implantation is sharply defined. The filamentous strands of pigment reflect brightly against the nondescript background.

Darier [2] noted that argyria may be encountered in the mouth as localized spots resulting from cauterization with silver nitrate. In discussing generalized argyria, he stated that the pigment granules chiefly impregnated the elastic fibers and capillaries and were absent from the cellular elements. In amalgam tattoo no pigment has been observed in the blood vessels, probably because the pigment is not carried to the tissues by the blood as it is in generalized argyria. However, it does appear from the morphology of the process that the silver is picked up by the elastic fibers, producing the filamentous picture.

ADDENDUM

Since this article was submitted for publication, one other reference was found.[3] Here again the affinity of silver for the elastic fibers is stressed.

2. Darier, J.: Précis de dermatologie, Ed. 4, Paris, Masson & Cie, 1928, p. 435.

3. Joseph, M., and Van Deventer, J. B.: Atlas of Cutaneous Morbid Histology, Chicago, W. T. Keener & Co., 1906, p. 5.

METASTATIC BUBO IN LYMPHOGRANULOMA VENEREUM

RONALD G. SIMPSON, M.D.(Aberdeen), M.R.C.P.(London)
ABERDEEN, SCOTLAND

Although discrete polyadenopathy is known to occur in a minority of cases during the early stages of the bubonic form of lymphogranuloma venereum, the appearance of a fully developed bubo at a site remote from that of the original inguinal bubo is probably extremely rare. Cases with lymphogranulomatous inguinal buboes have been described with evidence of widespread involvement of retroperitoneal lymph nodes extending as far as the diaphragm (Reichle and Connor [1]) or of the mediastinal group of nodes (Sheldon et al.[2]).

The present case, in which a suppurating bubo appeared in the neck of a patient with bilateral inguinal buboes, is reported because of the unusual features presented. It was the only one of its kind encountered by me in an experience of several hundreds of cases of bubonic lymphogranuloma venereum in India, and the rarity of this manifestation of the disease is further suggested by the fact that only seven other similar examples have been recorded in medical literature (Chevallier and Barreau,[3] Skorpil,[4] Kornblith,[5] Eberhard,[6] Melczer and associates,[7] Costello and Cohen,[8] and Manson-Bahr [9]).

REPORT OF A CASE

The patient was a British soldier, aged 28 years, who had previously been in good health. He came into my care in November, 1945, because of swellings of some two months' duration in the right side of the neck and both groins. Approximately four months before I saw him, he had had normal coitus with a Burmese girl. No symptoms of any kind were noted until two months later, when swellings appeared almost simultaneously in both groins and in the right side of the neck. They were practically painless and increased steadily in size during the ensuing three weeks. At the end of this time both groin swellings ruptured through the skin and discharged small amounts of a yellowish semifluid material; the skin over the swelling in the neck remained intact.

Because of frequent movements from one station to another on his journey from Burma to Southern India, several weeks elapsed after the onset of symptoms before the patient was able to report at a military hospital. At the time of admission to the venereal diseases unit he was afebrile and did not complain of any symptoms. There was a firm mass of matted lymph

1. Reichle, H. S., and Connor, W. H.: Lymphogranuloma Inguinale: Report of Case with Involvement of Retroperitoneal Lymph Nodes and Probable Involvement of Hip Joint, Adrenals and Kidneys, with Autopsy, Arch. Dermat. & Syph. **32**:196 (Aug.) 1935.

2. Sheldon, W. H.; Wall, M. J.; Slade, J. DeR., and Heyman, A.: Lymphogranuloma Venereum in Patient with Mediastinal Lymphadenopathy and Pericarditis: Isolation of Virus from Supraclavicular Lymph Node, Arch. Int. Med. **82**:410 (Oct.) 1948.

3. Chevallier, P., and Barreau, P.: Adénopathies inguinales vénériennes non suppurées avec généralisation transitoire à des groupes ganglionnaires (forme non-suppurée et extensive de la maladie de Nicolas et Durand), Bull. Soc. franç. dermat. et syph. **32**:177, 1925.

4. Skorpil, F.: Case of Inguinal Lymphogranulomatosis with Rare Complication and with Determined Source of Infection, Časop. lék. česk. **73**:157, 1934.

5. Kornblith, B. A.: Lymphogranuloma Venereum; Report of Case with Glandular Enlargement and Hepatosplenomegaly, J. Mt. Sinai Hosp. **3**:24, 1936.

6. Eberhard, T. P.: Generalized Lymphogranuloma Inguinale, Ann. Surg. **107**:380, 1938.

7. Melczer, M.; Sipos, K., and Venkei, T.: Mit schweren Allgemeinerscheinungen vergesellschaftetes, extragenitales, zum Tode führendes Lymphogranuloma inguinale, Arch. Dermat. u. Syph. **178**:124, 1938.

8. Costello, M. J., and Cohen, J. A.: Lymphogranuloma Venereum Affecting Simultaneously Cervical and Inguinal Lymphatic Glands: Report of Case, Arch. Dermat. & Syph. **41**:557, (March) 1940.

9. Manson-Bahr, P.: The Dysenteric Disorders: The Diagnosis and Treatment of Dysentery, Sprue, Colitis and Other Diarrhœas in General Practice, Ed. 2, London, Gilbert Wood & Company, Ltd., 1943.

nodes 2 in. (5 cm.) in diameter just below the angle of the mandible on the right side, and a mass of discrete nodes was present in the right axilla. In the medial portion of each groin there was a bubo measuring 2 in. in the long axis; the skin overlying the inguinal buboes showed some bluish discoloration and several small sinuses from which a small quantity of seropurulent material could be expressed. Finally, well-marked discrete enlargement of the external iliac lymph nodes was present on the left side. There were neither signs nor history of septic foci or sores in the respective regional lymph-drainage areas of the affected groups of nodes.

A detailed general physical examination disclosed no other important abnormalities, and the findings on a rectal examination were negative.

Laboratory Data.—Urinalysis was negative for albumin and sugar. Blood studies showed 90% hemoglobin; 4,800,000 red blood cells per cubic millimeter, and 7,600 white blood cells per cubic millimeter, consisting of 65% polymorphonuclear neutrophiles and 35% lymphocytes. The erythrocyte sedimentation rate was 42 mm. in one hour (Wintrobe). The total serum proteins amounted to 8.6 gm. per 100 cc. and the albumin-globulin ratio was 0.56:1. The Paul-Bunnell test for heterophile antibodies was negative, as were the results of serologic tests for syphilis. The intradermal Frei test with yolk-sac antigen (Lederle) gave a strongly positive response on each of two separate occasions, with no reaction at the control sites. A chest roentgenogram showed a prominent hilar shadow on the left side but otherwise the findings were negative. The semifluid matter expressed from the groin sinuses was examined; no pyogenic bacteria or tubercle bacilli were discovered, and the cultures were sterile. Stained films showed numerous degenerated polymorphonuclear leucocytes. These findings also applied to material of a similar nature obtained from the submandibular bubo by needle aspiration.

Clinical Course.—It was felt that the diagnosis of lymphogranuloma venereum was reasonably complete, and the patient was treated with sulfathiazole to a total dosage of 42 gm. orally over 10 days. Three weeks after the commencement of chemotherapy, only a few small nodules could be detected at the sites of the three former buboes, and the groin sinuses had completely healed; the enlarged lymph nodes in the right axilla had become very much smaller, and the external iliac nodes were no longer palpable. A further roentgenogram of the chest showed normal hilar shadows; the erythrocyte sedimentation rate was 6 mm. in one hour, and the total serum proteins were 8.0 gm. per 100 cc., with an albumin-globulin ratio of 1.28:1. Four months later the patient was in perfect health and there were no signs of recrudescence of the disease.

COMMENT

It is believed that this case provides a further example of metastatic bubo developing in a patient with the usual inguinal bubonic form of lymphogranuloma venereum. The possibility of simultaneous genital and oral inoculation of the infection with spread to the inguinal and cervical lymph nodes, respectively, has been fully considered, but it seems to be highly improbable. It is well known that oral infection with this disease can result from sexual perversion (cunnilingus), but the patient, who was a dependable witness, repeatedly and emphatically denied indulgence in any such practice.

The mode of spread of the infection from the genital and inguinal regions to the neck must remain a matter for conjecture, and it must be presumed that the route was either by the blood stream or by the lymphatic channels via the thoracic duct and its tributaries. By reason of the selective involvement of widely separated groups of lymph nodes, the absence of constitutional symptoms, and the well-recognized lymphotropism of the lymphogranuloma virus, it is considered that the lymphatic route is the more likely one.

SUMMARY

A case of lymphogranuloma venereum with bilateral inguinal buboes and a metastatic bubo in the neck is described. This is a rare manifestation of the disease, and only seven similar examples have been reported.

48 Rosebery St.

Correspondence

BULLOUS VARIETY OF INCONTINENTIA PIGMENTI (BLOCH-SULZBERGER)

To the Editor.—In their excellent paper entitled "Bullous Variety of Incontinentia Pigmenti (Bloch-Sulzberger)" (A. M. A. ARCH. DERMAT. & SYPH. **65**:557-567 [May] 1952), Epstein, Vedder, and Pinkus state that they saw no signs of follicular atrophoderma upon examination of their patient at the age of 16 months. The authors, however, noted agenesis of the skin appendages in the histologic pictures of specimens taken at the ages of 19 days and one year.

Agenesis of skin appendages was noted in the histologic pictures of follicular atrophoderma of two girls observed by me (Curth, H. O.: Follicular Atrophoderma and Pseudopelade Associated with Chondrodystrophia Calcificans Congenita, *J. Invest. Dermat.* **13**:233-247 [Nov.] 1949) at the ages of 8 and 9 years, respectively. In the 9-year-old child and her 4-year-old sister incontinentia pigmenti was also present. I saw my patients with incontinentia pigmenti and their 37-year-old mother for the first time at an age when the preceding inflammatory process of the skin had been inactive for some time. Clinically, my patients presented peculiar skin dimples at the sites of the hair follicles. I considered the dermatosis to be follicular atrophoderma because Miescher (Atypische Chondrodystrophie, Typus Morguino, kombiniert mit follikulärer Atrophodermie, *Dermatologica* **89**:38-40 [Jan.-Feb.] 1944), who was the first to describe this condition, had called it "*follikuläre Atrophodermie.*" Epstein, Vedder, and Pinkus, however, are correct in pointing out that absence of the appendages is due to agenesis rather than atrophy. Among other congenital defects, atrophic alopecia of the scalp (pseudopelade) was present in the authors' and my cases.

Since Epstein, Vedder, and Pinkus' histologic pictures suggest below a layer of hyperkeratosis slightly sunken-in surfaces of structures resembling sweat duct openings, I believe that the authors may have dealt with a process of the same order but perhaps of less intensity than the one which caused permanent skin dimples in the patients whom I observed.

HELEN OLLENDORFF CURTH, M.D.
35 E. 84th St.
New York 28, N. Y.

Society Transactions

CLEVELAND DERMATOLOGICAL SOCIETY

George H. Curtis, M.D., *President*
John R. Haserick, M.D., *Secretary*
Harold N. Cole Jr., M.D., *Reporter*
Jan. 24, 1952

Case for Diagnosis: Henoch's Purpura? Presented by DR. GEORGE H. CURTIS and (by invitation) DR. G. D. CHIRELLI, Parkman, by courtesy of DR. JOHN BATTLE of the Medical Department, The Cleveland Clinic.

W. H. M., a white man aged 38 years, was admitted to the Cleveland Clinic on Sept. 7, 1951, with the complaint of an eruption on the arms and legs of one year's duration. This consisted of multiple erythematous papules which became brown and occasionally formed crusts. Associated with the eruption was aching of the arms, elbows, fingers, knees, legs, and ankles. The cutaneous manifestations and general symptoms occur in cycles of approximately two weeks. With the more recent episodes there have been gastrointestinal symptoms of abdominal pain, nausea, emesis, and constipation. There was a weight loss of 20 lb. (9.1 kg.) during the six months prior to admission.

The general physical examination reveals no abnormalities, except for slight edema of the ankles, with moderate tenderness. There are an ulcer on each leg and many scars of former lesions, one with a purpuric center. About the ankles are numerous petechiae and purpuric macules up to 1 cm. in diameter. A few with vesiculopustular centers are present. Several have ulcerated. On the right forearm is a hand-sized, light yellow-tan area, the site of a subsiding lesion. There are also purpuric lesions on the plantar and dorsal surfaces of the feet.

The hemogram was normal. Thrombocyte (platelet) count and bleeding and coagulation times were normal. The roentgenograms of the chest, gall-bladder, esophagus, stomach, duodenum, and colon were normal. The stool examination revealed considerable mucus, but only a 1 + reaction for occult blood. The urinalysis revealed nothing abnormal. Serum proteins were normal. The Wassermann and Kahn reactions of the blood were negative. The sedimentation rate was only slightly elevated.

Sections of skeletal muscle on microscopic examination revealed in one section a small vessel infiltrated by neutrophiles, lymphocytes, and occasional eosinophiles. There was a fibrinoid change of the vessel walls. Some of the muscle cells showed necrosis and infiltration by neutrophiles. In other sections there were isolated muscle cells, which were necrotic and infiltrated by neutrophiles.

A microscopic section from the anterior surface of the right leg showed the epidermis to be uninvolved, except for a slight parakeratosis. There was diffuse extravasation of erythrocytes throughout the entire upper cutis. A few polymorphonuclear leucocytes were seen scattered throughout the same area. Large masses of polymorphonuclear leucocytes were seen around the deeper blood vessels and accessory glands. There was extravasation of erythrocytes deeper in the cutis at the level of the hypodermis.

The patient was given an elimination diet in an attempt to reproduce an attack. During the observation period in the hospital there has been no new episode. Except for scars, there are no new skin lesions at this time.

DISCUSSION

DR. GEORGE H. CURTIS: This case is very interesting because it has proved a problem in diagnosis. This patient is one of Dr. John Battle, of the Medical Service. Dr. Battle studied him most thoroughly from the standpoint of all the blood dyscrasias and the lymphoblastomas. Under our observation he has had three attacks, although they did not occur while he was in the hospital. They consist of malaise, nausea, vomiting, abdominal cramps, and, with one attack,

definite signs of blood in the stools. The eruption is purpuric. On two occasions he has noted an urticarial type of eruption, with nodular lesions near the knee joints and on the wrists. Since he has been thoroughly searched from the standpoint of foci of infection, including gall-bladder drainage and culture, which was sterile, we are at a loss to determine exactly the cause of this syndrome. The syndrome fits in very well with Henoch's purpura. We started him on an elimination diet for a week and then gradually added foods every three days. He came in about every week or 10 days, and I outlined new foods for him to add, which he did. When he got to milk and cheese he had an attack on the second day. That attack subsided, and he was brought into the hospital. We immediately put him back on an elimination diet and worked him back up to milk and cheese again, and nothing has happened.

Dr. A. L. Leiby, Akron: I should like to offer the suggestion that he be allowed to return home and repeat the same procedure.

Dr. B. Levine: I agree that environment is important, and in matters pertaining to allergy I think that house dust plays a very important part. It is the house dust plus the specific food that will cause the eruption. When the house dust is eliminated, as in the hospital, then the food is tolerated, but when both are present the patient will get the allergic reaction. I think that he is allergic to milk and cheese, plus house dust.

Dr. John R. Haserick: I believe that the allergists have a term "pyramiding." I have a friend, an allergist, who can eat lemons, but exposure to lemons plus ragweed causes him to have a high fever. If he avoids lemons, he does not get this pyramiding reaction. Over the years he has worked this out, and it might apply in this case.

Dr. J. A. Gammel: What accounts for the scarring?

Dr. George H. Curtis: Some of the lesions have broken down to form ulcers. The patient was studied from the standpoint of periarteritis nodosa, with muscle and skin biopsies, but no such histologic changes have been observed.

Chronic Disseminated Lupus Erythematosus. Presented by Dr. John R. Haserick and (by invitation) Dr. F. J. Rogers.

A. C. L. M., a white man aged 30, was first admitted to the Cleveland Clinic on Jan. 21, 1952, complaining of an extensive dull red eruption on the face of some 12 years' duration. About 13 years ago he first noticed a "red blotching" on the cheeks while working in the desert in Idaho. Since that time there has been a variable but persistent and slowly spreading erythematous eruption on the face, ears, and scalp, and lately on the shoulders and chest. It is definitely aggravated by sunlight, clearing somewhat in the winter. There have been no significant systemic symptoms. The diagnosis of chronic discoid lupus erythematosus was made 13 years ago, and over the years bismuth, gold, and various other types of therapy have been tried, with generally disappointing results. Sixteen days of cortisone therapy caused a significant remission of lesions, which relapsed shortly after cortisone administration was discontinued.

There are extensive dull red, slightly atrophic areas with a fine adherent scale involving the cheeks, parts of the forehead, chin, and both ears. Two areas of similar lesions on the scalp, with alopecia, are present. Smaller discrete lesions of a similar type are present on shoulders and upper chest. The results of the general physical examination are normal.

Routine laboratory studies are incomplete. The plasma L. E. test is negative.

DISCUSSION

Dr. E. S. Hallinger: I should like to ask Dr. Haserick whether the L. E. test is always negative in the nonacute type of lupus erythematosus.

Dr. John R. Haserick: Yes, it is always negative in chronic discoid lupus and in about half the cases of the subacute disseminated type. I thought this was an interesting case clinically. I should like the opinion of the group in regard to treatment. One hates to use steroid therapy in a man so obviously healthy, and yet mental changes are developing.

Dr. Gerard A. De Oreo: There is much inflammation in this man's lesions. I think this is a case in which some of the antibiotics, such as aureomycin or a combination of aureomycin and chloramphenicol (chloromycetin®), might be helpful.

DR. H. A. HAYNES, Akron: I notice that he has had gold, bismuth, etc., and has not had a trial of vitamin E. We have had pretty good success in old cases with administration of vitamin E intramuscularly, 200 mg. once or twice a week.

DR. J. R. DRIVER: The color of this eruption is rather interesting. It is a very dull, reddish type of eruption, different, I think, from that in most of the cases we see. Has it always been this color, or did the color develop after the gold therapy?

DR. JOHN R. HASERICK: We did not see this man until two days ago. I have never asked him about that. He does use foundation lotions to cover the lesions, and I wonder whether irritation produces that change.

DR. H. N. COLE: It is my impression that the disease in this man is on the verge of dissemination into a true subacute type. The character of the dusky red eruption on the face suggests that to me.

DR. JOHN R. HASERICK: On the basis of that, would you feel justified in going ahead with steroid therapy?

DR. J. R. DRIVER: I think this is the type of chronic disseminated lupus which reponds best to vitamin E therapy. I have seen some spectacular results in this particular type.

DR. E. S. HALLINGER: There is one point which ought to be brought out. He is exposed to sunlight a great deal, and, although he does use a foundation lotion, I do not think that is enough to screen out the light rays. He should be warned to guard against exposure or change his occupation so that he is not exposed so much.

DR. JOHN R. HASERICK: I am inclined to agree with Dr. Cole that the condition in this man is advancing to systemic involvement. I think that we can now draw certain conclusions from our experience. I had occasion to follow six patients with weakly positive plasma L. E. tests; for each patient we discussed steroid therapy in much the same way we are discussing it now, and in each case treatment was not carried out. Four of those persons died within a year. Therefore, we have begun to think that such patients are perhaps in a more dangerous position than those with full-blown lupus erythematosus.

From November, 1948, to November, 1949, before cortisone was available, 9 of 10 patients in our series died of lupus erythematosus. The 10th, a patient of Dr. Netherton, has never had any cortisone and is apparently doing very well. From 1949 to 1951, we have had 38 such patients and only 8 have died. We feel that these figures alone are evidence that the patients are benefited by a maintenance program, as shown both clinically and by the laboratory results. We do not believe that acutely ill patients ever should be given short-term corticotropin or cortisone therapy, for I believe that the condition may be aggravated. They should be placed on a program of months' or years' duration.

Sarcoidosis and Cryptococcosis (Torula Meningitis). Presented by DR. GEORGE H. CURTIS and (by invitation) DR. G. D. CHIRELLI, Parkman, from the Medical Department, The Cleveland Clinic, through the courtesy of DR. J. A. ECKER.

J. H. R., a Negro housewife aged 33, was admitted to the Cleveland Clinic on Oct. 19, 1951. In 1948 enlarged mediastinal nodes were discovered and deep x-ray therapy was administered. This was followed by hemoptysis and then chronic cough and dyspnea. She was put to bed for six months, beginning in December, 1948. In March, 1950, the first lesion appeared on the scalp, and since then others have appeared on the scalp and right arm. The cough and attacks of hemoptysis and orthopnea have been progressive. There has been little or no weight loss.

On physical examination, indurated lesions with alopecia were seen on the scalp. The lacrimal and parotid glands are enlarged, and slight ptosis of the right eyelid is apparent. The submandibular, cervical, inguinal, and right epitrochlear lymph nodes are enlarged. Findings in the chest indicate evidence of widened mediastinum and pleural effusion of the left side. Roentgenograms show left pleural effusion, hilar mass and strands of increased density extending to the left upper lobe.

Blood studies revealed 4,020,000 red cells, with a hemoglobin concentration of 9.5 gm. per 100 cc., or 62%; the differential count showed 11,900 leucocytes, with 90% neutrophiles, 6% lymphocytes, and 4% monocytes. There were no sickle cells. The sedimentation rate was

2.2 mm. per minute (normal, 0.45 mm. per minute). The serum protein was 9.2 gm. per 100 cc., with 3.9 gm. of albumin and 5.3 gm. of globulin. The sputum and pleural fluid examinations for fungi, tubercle bacilli, and neoplastic cells were negative. Serum electrolytes were in normal amount. The Kveim test was positive. Tuberculin tests were negative.

Microscopic examination of a biopsy specimen showed the histologic picture of sarcoid.

Beginning on Oct. 30, 1951, streptomycin, 1 gm., was administered twice weekly, and sedatives and bed rest were prescribed. On Dec. 12, 1951, the scalp lesions showed definite recession. On Jan. 2, 1952, the patient was admitted to the hospital. Corticotropin was administered in 20-mg. doses every six hours, while use of streptomycin in 1-gm. doses twice weekly was continued. Three weeks prior to the hospital admission she began to have headache, and pain in the right eye had been constant. Neurologic examination showed hyperactive reflexes and the presence of Hoffmann's sign bilaterally. Ophthalmologic examination showed a normal condition and normal visual fields. On bronchoscopic examination no neoplasm was found. Because of the persistent eye pain, a lumbar puncture was done. The spinal fluid was cloudy, and on culture Cryptococcus neoformans was obtained.

Sarcoidosis. Presented by DR. GEORGE H. CURTIS.

This case was first presented before the Society on Feb. 23, 1951. T. L. W., a Negro housewife aged 26, was admitted to the clinic on April 21, 1950, complaining of an eruption of about two years' duration.

There are dark-colored papules and groups of papules of granulomatous type on the vermilion borders and cutaneous surfaces of the lips, alae nasi, medial and lateral canthi, eyelids, right posterolateral aspect of the neck, and the left buttock.

The urinalysis, hemogram, and blood chemical determinations (except for a reversal of the albumin-globulin ratio) showed nothing abnormal. Tuberculin tests with first- and second-strength purified protein derivatives were negative.

Chest roentgenograms, including progress films, were interpreted as being consistent with the diagnosis of sarcoidosis of mediastinal nodes and lung fields.

Microscopic examination of a biopsy specimen revealed the following: A thin laminated, vacuolar hyperkeratosis was present. The epidermis was normal, except for flattening of the rete pegs. Heavy pigmentation of the basal layer was present. Epithelioid cells in well-defined groups and in masses were localized beneath the epidermis and the upper corium. A few giant cells containing pigment were present. There was no necrosis, and almost no lymphocytes were seen around the tuberculoid reaction. A Langhans giant cell was present.

Two separate regimens of administration of vitamin D_2 (calciferol) rapidly produced an elevation of the blood calcium to 160 mg. per 100 cc., with nausea and vomiting. Sodium arsenate has been administered since September, 1950, and there has been a marked regression of the skin and mediastinal lesions.

At this time, there are no skin lesions and the chest findings have shown considerable regression.

Case for Diagnosis: 1. Pulmonary Tuberculosis with Tuberculous Adenitis? Tuberculous Peritonitis? 2. Generalized Sarcoidosis (Boeck) with Involvement of the Skin, Lungs, Hilar Lymph Nodes, Axillary Nodes, and Abdominal Viscera, with Peritonitis? Presented by DR. GERARD A. DE OREO, through the courtesy of DR. HAROLD CURTIS, Sunny Acres Sanitorium.

R. M., a Negro man aged 22, was admitted to Cleveland City Hospital on Feb. 6, 1951, because of fever and generalized lymphadenopathy. A roentgenogram of the chest showed a "healed primary complex"; examination of the sputum revealed no tubercle bacilli, and the patient signed a release from the hospital. On Feb. 28, 1951, he was admitted to Lowman Pavilion because of fever and a right pleural effusion. Repeated examinations of the sputum, as well as of the gastric washings, revealed no tubercle bacilli. A roentgenogram of the chest showed infiltration of the right subapical area and increased markings in the hilar region. Biopsy of a node from the right axilla showed "caseation consistent with tuberculosis." Stains for acid-fast bacteria revealed none. In November he was admitted to Sunny Acres Sanitorium

because of sudden abdominal pain and fever. A diagnosis of peritonitis was confirmed by roentgenography. The abdominal distress gradually subsided.

The past history is not significant.

The patient's parents and five siblings are living and well. There is no tuberculosis in the family.

Examination reveals a 22-year-old Negro in no acute distress. There are nodes in the cervical, axillary, and inguinal regions. The nasal mucosa is studded with firm papules. The tonsils are massive. On the face there are multiple firm papules involving the lids and cheeks. There are similar papules scattered over the arms and trunk.

The Kveim test on the right forearm shows a persistent nodule. The inoculation was made on Dec. 14, 1951. The reaction to first-strength purified protein derivative was positive. Roentgenograms of the fingers were normal. Results of a urinalysis were normal. A hemogram showed 14,100 white blood cells, with a differential count of 77% neutrophiles and 23% lymphocytes. The vital capacity is 55% of normal. The globulin is 2.4 gm. and the albumin 5.6 gm. per 100 cc.

Histologic sections of a lesion on the face showed a diffuse infiltration in the corium, with some separation by connective tissue septa. A stain for tubercle bacilli was negative. Histologic sections of a biopsy specimen taken from the site of the Kveim test showed granulomatous infiltration. The Verhoeff stain was negative for tubercle bacilli.

There has been no clinical improvement after 90 days of combined therapy with streptomycin, 1 gm. each day, and paraaminosalicylic acid.

DISCUSSION ON PRECEDING THREE CASES

DR. I. L. SCHONBERG: The cases of sarcoidosis presented give us some insight at least into the causation of sarcoid. One is a case of cryptococcosis associated with sarcoidosis, and another is of tuberculosis associated with sarcoid-like changes. Of course, there are other primary diseases which may produce a sarcoid type of reaction. These cases point to the fact that in all probability sarcoid is not in itself an entity but rather a reaction of the entire body to some organism, probably not a specific organism. I think that sarcoid is probably an allergic type of phenomenon.

DR. H. A. HAYNES, Akron: I believe that at the meeting of the Central States Dermatological Association, in Ann Arbor, Mich., last spring Dr. Curtis presented a case of cryptococcosis with meningitis, positive culture from the spinal fluid, and prolonged administration of sulfonamides plus penicillin.

DR. E. S. NETHERTON: What sulfonamide drug was used?

DR. H. A. HAYNES, Akron: I think sulfadiazine, in very high doses for a long time, plus penicillin.

DR. GEORGE H. CURTIS: I should like to show the chest roentgenogram in the first case, that of sarcoidosis, cryptococcosis, and pleural effusion. I understand that this is a rare complication of sarcoidosis. I had done a considerable number of tuberculin studies, and all cultures had been negative for fungi, tubercle bacilli, and neoplastic cells. The smear had been negative for tumor cells. Bronchoscopy has also shown no evidence of a tumor.

DR. GEORGE A. DE OREO: I should like to make a comment on the last case, that of the 22-year-old man. This man has a long history. He has had three admissions. One was because of fever and generalized adenopathy. An axillary node was removed, and on the basis of the findings a diagnosis of Hodgkin's disease was entertained. On the second admission he had pleurisy with effusion, and that time he was thought to have tuberculosis. Sputum tests, etc., were all negative, but the tuberculin test was positive. The third time he had an acute peritonitis. It was thought to be a tuberculous peritonitis, but all tests were negative. Months ago the skin lesions you saw today, the waxy, firm papules, developed on the face. The Kveim test was done, and a positive reaction was elicited.

My own impression is that this man has one disease, not tuberculosis at all, and that all his complaints are based on a single condition, namely, sarcoidosis. I think that it is important, because he has been in the hospital now for 100 days, receiving a combination of streptomycin, 1 gm. daily, and paraaminosalicylic acid, without any effect on his disease. I should like someone else's opinion.

DR. E. S. NETHERTON: I agree with Dr. De Oreo's remarks. I think that our view of these conditions in Negro patients should always be somewhat different from that in the white patients, because Negroes frequently have tuberculosis and eventually show sarcoid. Sarcoid in this type of patient is not absolutely the same as sarcoid in the white patient. In the first case I look on the Cryptococcus meningitis as coincidental. I do not think that the sarcoid is due to the Cryptococcus infection. You took biopsy specimens from the ulcerated lesions. I wondered if you noticed any yeast-like cells in lesions on the surface of the ulcers. I believe that she had Cryptococcus meningitis and sarcoid, the one not necessarily complicating the other, but two different things.

DR. GEORGE H. CURTIS: I should like to go back to the patient with Cryptococcus meningitis. Her sarcoidosis was discovered in 1948 on the basis of enlarged mediastinal nodes and some infiltration in the lung fields. The symptoms of cryptococcosis did not appear until about the middle of December, 1951, which was approximately three years later. Seventy-two hours ago she was comatose and could not be aroused. In the past 72 hours she has had periods when she seems lucid and recognizes people and talks to them, although she continues to complain of pain in the head. She has received sulfadiazine, urea, and potassium iodide in large doses, aureomycin, quinacrine hydrochloride (atabrine® dihydrochloride), actidione® (a derivative of Streptomyces griseus), 20 mg. twice daily, and undecylenic acid in 4-mg. capsules twice daily. I realize that, on the face of it, this massive therapy seems silly, but we are dealing with a fatal disease. If I had this disease, I would not care if somebody gave me 50 different drugs if they would bring me out of it. Two cases have been reported of cryptococcosis treated with actidione® (Wilson, H. M., and Dureyea, A. W.: *A. M. A. Arch. Neurol. & Psychiat.* **66**:470 [Oct.] 1951). One patient died within one month, and one was alive at the end of 20 months' observation. That is the reason we are giving actidione,® which is one of the new antibiotics.

Cheilitis Exfoliativa. Presented by DR. GEORGE H. CURTIS and (by invitation) DR. F. J. ROGERS.

J. P. T., a 26-year-old white woman, was admitted to the Cleveland Clinic on Aug. 21, 1951, complaining of crusting of the lips of 20 years' duration and red, swollen, bleeding gums of 5 years' duration.

All efforts to find contact allergens have failed. She denies taking drugs other than those prescribed for this condition. Since the onset at the age of 6 years, no treatment has helped to any significant degree.

When the patient was first seen, there was a thick crusting of the lips, which, when peeled off, exposed a red, smooth, shiny surface. The upper gums were red and boggy. No pus could be expressed from the lips or the gums, and no visible glandular orifices were noted. Dental examination disclosed five carious teeth.

On laboratory study the hemogram and urinalysis gave normal results. The blood Wassermann and Kahn reactions were negative. The blood sugar level was 71 mg. per 100 cc. Endolimax nana was found on stool examination. Roentgenograms of the teeth showed no evidence of focal infection.

A biopsy was refused by the patient. Cultures of crusts from the lips revealed growth of a saprophytic fungus.

DISCUSSION

DR. B. LEVINE: The history of this patient shows that she was one of five children. Their food was very poor. She said that in her youth there were many days that she did not have enough to eat. She told me that this ailment dates back to her childhood. I think that it is a case of riboflavine deficiency. Even though her diet is adequate in her adult life, all of us know that when a vitamin deficiency has developed it takes enormous doses of the vitamin to overcome it, far more than anyone would get in her diet. I suggest intramuscular injections of riboflavine, vitamin B_2, and vitamin B_{12}, at least 30 γ per injection, large doses of vitamin B complex, and at least 10 to 15 gm. of riboflavine, three times a day, augmented with intramuscular injections of vitamin B_{12}. She has a smooth, glossy tongue margin, gingivitis, and cheilitis, and I think, by overcoming the vitamin deficiency with vitamin B complex therapy, that she probably can be cured.

DR. I. L. SCHONBERG: It is still difficult on examining this patient to rule out the possibility of a contact dermatitis. In spite of the fact that the history states that all tests for allergens are negative, there is one test which should be done, if it has not already been done. In the past two years I have seen two patients highly sensitive to mercury. Because they had amalgam in the teeth, they had a dermatitis of the mouth and lips. This patient did have trouble with the lips prior to the time the amalgam fillings were put in. She may have had a mild cheilitis which was aggravated by the presence of amalgam fillings. She should be tested for mercury sensitivity.

DR. B. LEVINE: Twelve or 14 years ago Dr. Netherton presented a case in which the final treatment was electrodesiccation of the lips, with good results. That patient was 9 or 10 years old. All tests, including those for Candida (Monilia), had been negative, and finally in desperation this procedure was carried out.

DR. E. S. NETHERTON: I recall an article by Woodring on a case of cheilitis almost identical with this one, and he pointed out that the condition was on a psychogenic basis. The patient was a physician's daughter and had a neuropsychiatric problem. Through the help of psychiatrists, considerable improvement was brought about.

DR. GEORGE H. CURTIS: This patient is a most intelligent person and gives a long history of poverty. She recently moved here from Pittsburgh. She visited the clinics there for years, and no one was ever able to do her any good.

DR. G. M. STROUD: This patient's personality impressed me as being what psychiatrists call the oral type. Dr. Harvey Blank, in the Psychosomatic Symposium, at the meeting of the American Academy of Dermatology in Chicago last December, found this personality type, with traits of dependency, to be present in a series of cases of recurrent herpes labialis. Two psychiatrists on the same program pointed out the differences, in connection with psychotherapy, in patients who manifest a degree of dependency. I think a psychiatric evaluation is in order, however. Empirically I recommend, inasmuch as the process is fissured and hyperkeratotic, the use of vitamin A cream.

DR. J. E. RAUSCHKOLB: I am impressed with the localization of this inflammatory process to the anterior part of the mouth and the lips. I took considerable time to examine this patient, and I found that the mandibular half of the lingual surface of the periodontal membranes is perfectly normal; so, too, are the buccal mucosa and the posterior part of the tongue. There is no inflammatory process on the posterior part of the tongue or on any part inside the mouth proper. The inflammatory process, as I saw it, is localized to the perigingival mucous membranes of both the alveoli and the mandibular half, probably from the first bicuspid around to the opposite side. The lips are completely involved. On the tip of the tongue and along the anterior margin there is some edema, but it is not that seen in vitamin deficiency diseases. Either this lesion is on an inflammatory basis superimposed on a contact dermatitis, due to the usual instruments for feeding, or oral hygiene, or it represents a case of frank dermatitis factitia. To me it is not an avitaminosis or constitutional disease, but a condition provoked primarily by irritation.

DR. H. J. PARKHURST, Toledo: I think this is a contact dermatitis and that the question of the particular tooth paste that she is using should be carefully scrutinized. The methyl-salicylate in some pastes and the coloring and flavoring in others would have a distinct bearing, even to absorption by the mucous membranes. I would have her eliminate the use of all of them and use salt and soda.

Case for Diagnosis. Presented by DR. ALLEN E. WALKER, Bay Village, and DR. JOHN J. STEWART.

D. N., a 19-year-old white youth, first noted the onset of an eruption on the medial aspect of both knees four months ago, following trauma to these areas, which consisted of irritation secondary to kneeling and working in cement. He denies the use of medicaments and states that his general health has been excellent. He has noted that ordinary abrasions of the skin appear to be delayed in healing and seem to form a noticeable scar.

His past history is essentially noncontributory. He denies allergies.

On the medial aspect of both patellar areas are similar plaques, which measure approximately 5 cm. in diameter. The plaques are reddish and violaceous. There are whitish areas which are

atrophic, thin, and shining, with the violaceous component slightly elevated, indurated, and having a tendency toward annular configuration. The lesions are very sharply outlined. Results of the remainder of the physical examination are noncontributory.

A hemogram revealed the red blood cell count to be 5,100,000 per cubic millimeter, with a hemoglobin concentration of 92% (13.2 gm.), and 7,500 white blood cells. The differential count showed 54% polymorphonuclear leucocytes, 38% lymphocytes, 4% eosinophiles, 3% basophiles, and 1% monocytes. The Kline serologic test of the blood was negative. Results of a urinalysis were normal.

Histologic examination of a microscopic section from one of the lesions revealed an epidermis which was flat in some areas. There was slight hyperkeratosis and some associated increase in prominence of the granular layer. The section was not very thick and included only the pars papillaris and upper corium, which revealed a very granular, somewhat friable collagen, with some sections showing fibroblastic proliferation. There was rather striking thickening of all the capillaries, and some toxic hyalin was observed. The infiltrate was not marked and was definitely perivascular. It consisted of histiocytes, round cells, and polymorphonuclear leucocytes.

DISCUSSION

DR. H. A. HAYNES, Akron: I should like to suggest the diagnosis of Ehlers-Danlos syndrome.

DR. I. L. SCHONBERG: I want to agree with that diagnosis. In addition, I found that when the patient got down on his knees the point of pressure over the patella was not involved. Apparently the point of greatest pressure was the head of the tibia. It is probably a malformation of elastic tissue and gives rise to marked pseudotumors.

DR. ALLEN E. WALKER, Bay Village: We considered a number of conditions. When we first saw the patient, we thought of the possibility of an atrophic form of lichen planus. The lesion was violaceous and somewhat atrophic and occurred in areas of trauma, but the biopsy did not seem to bear this out. We also thought of the possibility of erythema elevatum diutinum. I think the histologic changes could fit in with this diagnosis. These changes are seen in certain cases of Ehlers-Danlos syndrome, and erythema elevatum diutinum might be found associated. I also considered the possibility of the lesions being a granuloma. Microscopically there was much thickening of all the capillaries in the pars papillaris and upper corium. There was also a fairly marked infiltrate, definitely perivascular in nature. I think Ehlers-Danlos syndrome is the best possibility.

Acanthosis Nigricans. Presented by DR. E. W. NETHERTON and (by invitation) DR. G. D. CHIRELLI, Parkman.
Exfoliative Dermatitis. Presented by DR. GEORGE H. CURTIS and (by invitation) DR. G. D. CHIRELLI, Parkman.
Basal-Cell Carcinoma (Superficial Type) Occurring in Vaccination Scar. Presented by DR. GERARD A. DE OREO.
Case for Diagnosis: Erythema Annulare? Presented by DR. E. W. NETHERTON and (by invitation) DR. F. J. ROGERS.
Pruritus of Pregnancy. Presented by DR. GEORGE H. CURTIS.
Mycosis Fungoides. Presented by DR. E. W. NETHERTON and (by invitation) DR. G. D. CHIRELLI, Parkman.
Dermatitis Herpetiformis. Presented by DR. JOHN R. HASERICK and DR. E. S. KOZIKOWSKI, Garfield Heights.
Urticaria Pigmentosa. Presented by DR. GERARD A. DE OREO.

George H. Curtis, M.D., *President*
John R. Haserick, M.D., *Secretary*
Harold N. Cole Jr., M.D., *Reporter*
Feb. 28, 1952

Epidermolysis Bullosa Dystrophica; Moderately Advanced Pulmonary Tuberculosis, Inactive. Presented by DR. GILBERT BARNES, DR. WOODROW MURPHY, and DR. BERT L. PEPPERCORN, for DR. JOHN E. RAUSCHKOLB.

M. P., a white man aged 46, was first seen in City Hospital in September, 1938, with a history of having had a bullous eruption of his skin since birth. He has had numerous admissions to hospitals in Cincinnati and Chicago.

There is no history of any similar eruption in the family, including the mother, father, and siblings.

On examination there are discrete, superficial ulcers, with crusts and purulent exudate, over the knees and pretibial areas, elbows, shoulders, lower back, and buttocks. The skin over the anterior tibial region is erythematous, dry, and thickened. The nails are absent; the fingers are fused and fixed in flexion contracture. There are scattered bullae over the extremities. The cornea of the right eye is occluded by thick white scarring.

The results of urinalysis were normal. Examination of the urine for porphyrins revealed no fluorescence under Wood's light. No chloroform-insoluble compound was present on the test with Ehrlich's aldehyde reagent. The hemogram revealed 3,630,000 erythrocytes, with 11 gm. of hemoglobin, and 10,800 leucocytes, with 83% polymorphonuclear cells, 14% lymphocytes, 2% monocytes, and 1% eosinophiles. A blood serologic test was negative.

The fasting blood sugar was 76 mg. per 100 cc. The blood cholesterols were 104 mg. and cholesterol esters 52 mg. per 100 cc. The total protein was 7.6 gm. per 100 cc., with 3.4 gm. of albumin and 4.2 gm. of globulin. The serum calcium was 10.1 mg. and the inorganic phosphorus 3.6 mg. per 100 cc. The result of the sulfobromophthalein (bromsulphalein®) sodium test and the prothrombin determination were within normal limits.

A recent roentgenogram of the chest revealed "moderately advanced pulmonary tuberculosis, which has shown marked regression during a 10-year period. There is no evidence of activity." Roentgenograms of the hands, feet, and skull showed no abnormalities. Sputum examinations disclosed no acid-fast bacteria.

Histologic examination of a biopsy specimen revealed separation of the epidermis from the dermis. The cleft was filled with blood cells. The dermis contained numerous small foci of lymphocytes and increased fibrous tissue.

Treatment has consisted of administration of penicillin procaine, 600,000 units daily, débridement of lesions, potassium permanganate soaks, and silver nitrate (1:1,000) soaks.

DISCUSSION

DR. H. N. COLE JR.: I do not dispute the diagnosis of epidermolysis bullosa, but I think that in addition this man presents a number of interesting features. When I first saw him in the clinic, the lesions over the extensor surfaces of the arms and anterior tibial region resembled in many ways a congenital ichthyosiform erythroderma. Also he had a diffuse keratoderma over the soles and a flexion contraction deformity of the fingers. In addition, there was a great deal of pityriasis of the scalp, which, of course, could accompany congenital ichthyosiform erythroderma. I think that he does have certain elements suggestive of an osteochondrodystrophy. The skull presents a peculiar shape. It has a flat top and comes to a point in back, rather suggestive of scaphocephaly.

Case for Diagnosis: Sarcoidosis with Hypoparathyroidism? Presented by DR. JOHN R. HASERICK and (by invitation) DR. F. J. ROGERS.

V. H., a 49-year-old Negro housewife, was admitted to the Cleveland Clinic on Feb. 13, 1952, with the chief complaint of tumors on the skin. She had been well until 1939, when at the age of 36 a lesion appeared on the right side of the face, following the "flu." Shortly after the onset hoarseness developed. During the next few years asymptomatic nodules and plaques appeared on other areas of the face, arms, and upper trunk. In 1944 a tracheotomy was performed, and the patient was told that tumors similar to those on her skin were "in her windpipe." She received injections at several institutions, with little effect on the lesions. During the past few years, new lesions have appeared over the phalangeal joints.

The patient's history prior to 1939 is noncontributory. There is no known significant family history.

The patient feels generally well. The skin lesions are asymptomatic. She has had a chronic cough, productive of small quantities of whitish mucus, for the past two or three years. There is slight dyspnea on exertion. Mild ankle edema has been noted for the past two years. The history by systems was noncontributory.

When first seen, the patient was well nourished and in no evident distress. There was a mild cough, with slight whitish sputum emitted from a tracheotomy tube. The temperature was 98 F. and the pulse rate 90 per minute.

The face was grossly distorted by very large, fleshy, brownish-red, nonulcerated nodules. These were present on the forehead, nose, ears, and cheeks. The lower lip was enlarged and protruded extensively. Similar but smaller nodules were present on the arms, hands, fingers, upper trunk, and legs. The fingernails were friable and broken. None of the lesions was anesthetic.

The blood pressure was 230/125. A soft apical systolic murmur was present. The liver was questionably enlarged 1 fingerbreadth on inspiration. The spleen was not palpated. The results of physical examination otherwise were normal.

Hemoglobin determination revealed 10.6 gm. per 100 cc. The erythrocyte count was 4,400,000 and the leucocyte count 5,100, with 59% neutrophiles, 24% lymphocytes, 11% monocytes, and 3% eosinophiles. The sedimentation rate was 1.6 mm. per minute (normal, 0.3 mm. per minute). Urinalysis revealed a specific gravity of 1.020, with occasional red blood cells and white blood cells noted. The blood chemical values were as follows: Serum proteins were 10 gm. per 100 cc., with 2.8 gm. of albumin and 7.2 gm. of globulin. Fasting blood sugar was 60 mg. per 100 cc. Blood urea measured 30 mg. per 100 cc. Cholesterol (plasma) was 162 mg. per 100 cc. The Wassermann and Kahn reactions of the blood were negative.

Special tests performed after three days of Aub diet gave the following results: The Sulkowitch reaction was 1+. Calcium excretion in the urine was 3.9 mg. per 100 cc., or 60 mg. total for one day's excretion of 1,530 cc. Urea clearance was 65% in the first hour and 50% in the second hour.

Sternal marrow examination revealed nothing abnormal. The electrocardiogram showed minor nondiagnostic deviations from normal.

Roentgenograms were reported as follows:

1. Chest (Feb. 15, 1952): The bony thorax was normal. The cardiac silhouette was within normal limits. Both hilar shadows were prominent and prominence of markings extended into both bases. The tracheotomy tube was visible. Calcifications of the arch of the aorta were present.

2. Both hands: Similar changes were noted in each hand. Rather marked soft tissue swelling of all the fingers, not entirely confined to the joint areas, was present. There were destructive lesions in the ends of the small bones. Joint spaces were narrowed. The terminal phalanges of the second fingers, right and left, were destroyed, the destruction appearing from within the shaft of bone. The changes were diagnosed as "consistent with sarcoidosis."

A Kveim test was done on Feb. 15, 1952, on the dorsum of the right hand. A Wade scraped incision smear for acid-fast bacteria from a lesion on the left ear lobe was negative. The reaction to a tuberculin test, done on the right forearm on Feb. 26, 1952, using 1:1,000 and 1:10,000 dilutions, was negative.

DISCUSSION

DR. H. HECHT: This is a very unusual case. I am sure that everyone who saw this case thought it was one of lepra tuberosa. The expression of the face is that of leprosy, but the histologic picture is not; it is one of sarcoidosis. I think that we should look further to see if there is leprosy. The patient was never outside the United States, although it is possible to get the disease in the South. The probability is that the condition is sarcoid, as far as we know.

DR. G. M. STROUD: I recall a case which was similar, but the condition was not as severe as in this case. The discussion revolved around the same point Dr. Hecht brought out, whether the disease was sarcoidosis or leprosy.

DR. H. H. JOHNSON: I remember that case very distinctly. We had a resident in pathology who had been in Egypt. He had seen many cases of leprosy, and he maintained that it was leprosy. That was before the days of the Kveim test.

DR. JOHN R. HASERICK: We, of course, were up against that same problem when we first saw this patient. Fortunately one of the rhinologists remembered a case in the otolaryngologic literature and found that it involved the same patient. The histologic features in that article were much more typical of sarcoidosis than those we found, and we felt that this helped us a great deal. Also, her Kveim test appears as if it were going to be positive, and the area is already starting to indurate. There is a recent article on Kveim tests in true leprosy, and their results were all negative. Along this same line, two or three years ago I had the opportunity to send some sarcoidosis sections to Dr. Fike, in Carville, La., because he was interested in

knowing whether he could tell sarcoid from leprosy. I also sent one slide of true leprosy, and he was able to make the diagnosis and to say that that was the only leprosy slide. We felt that he was accurate, and yet in the sarcoidosis slides he was unable to demonstrate anything he thought was leprosy. In this patient, incidentally, treatment is being started with calciferol. The hypoparathyroidism has been demonstrated to the satisfaction of Dr. Schneider, of the Department of Endocrinology. If this were leprosy, it would be of the lepromatous type and the lesions would be loaded with organisms. We have made serial sections and have studied them at length but have been unable to demonstrate Mycobacterium leprae.

DR. H. N. COLE: In leprosy is there a reversal of the albumin-globulin ratio as striking as in this patient?

DR. JOHN R. HASERICK: Occasionally, yes. There are also occasionally false positive reactions to tests for syphilis, etc.

Superficial Epitheliomatosis (Generalized); Keratoses, Arsenical in Origin (Palms and Soles). Presented by DR. JOHN E. RAUSCHKOLB.

F. L., a white man aged 60, has been under observation since July, 1937, because of numerous crusted lesions on the body and warts on the palms and soles. He consulted a physician initially on July 24, 1937, complaining of numerous lesions, 1 to 4 cm. in size, of a brownish-red color, with crusts, scattered over his body. These were of 20 to 25 years' duration. The condition was called psoriasis, for which potassium arsenite solution (Fowler's solution) was prescribed.

Examination reveals numerous superficial and multiple discoid, crusted epitheliomata, measuring 1 to 4 cm. in size and diameter. There are numerous arsenical keratoses on the palms and soles.

The histopathologic report on a biopsy specimen from one of the lesions, clinically interpreted as being an epithelioma, revealed the following: "There is a change in the epidermis to atypical cells. These occupy the entire thickness of the epidermis. The cells vary in size. Most are basophilic. In a few places there are multinucleated cells. Mitotic figures are abundant. Many are atypical. Some of the cells are moderately vacuolated. There is focal keratinization deep to the surface. There are marked hyperkeratosis and parakeratosis. In the cutis there is infiltration of lymphocytes and plasma cells. There is a margin of uninvolved tissue on all sides of the tumor, although the clearance is very narrow in one place. The diagnosis is intraepidermal carcinoma, Bowen type."

DISCUSSION

DR. H. HECHT: This is a very interesting case. Originally the diagnosis of psoriasis was made, and the physician prescribed potassium arsenite solution. The patient has arsenical keratoses now. I prefer to give injections because in Europe I saw several cases of widespread arsenical keratoses and epitheliomata followed by death. Therefore, I think this is another case which should show us that we must be very careful in prescribing arsenical preparations.

DR. H. H. JOHNSON: On questioning, this patient stated that he took potassium arsenite solution on only one occasion, for one month, starting with 3 drops, working up to 10, and then dropping down to 3. He states that that was the only time he took it, and his memory seems to be good for details. That seems to be a small amount of arsenic, relatively speaking.

DR. J. R. DRIVER: Dr. Rauschkolb, I believe that the history stated that these lesions were to be treated by contact x-radiation, which I think is probably the ideal method of treatment for this patient. I was wondering what dose you planned to give.

DR. JOHN E. RAUSCHKOLB: I have followed this patient for about 17 years. Originally his condition was diagnosed as psoriasis, and he was given potassium arsenite solution. Many of his lesions have been treated with carbon dioxide snow, and a good result was obtained. He has since refused that type of therapy. If one were to count his lesions, one would find 125 or more. About 10 years ago he came in with vegetating lesions, like some of these are becoming. I treated them with superficial irradiation, a total of 600 r to each lesion, over areas as large as a silver dollar, with good response. Those lesions are beginning to show telangiectasia, as one would expect. They are too extensive to excise. I am now using contact irradiation. The machine delivers 8,000 r per minute at 20 mm. In order to get a little penetration, I use it at 40 mm. Thus, he is getting 2,000 r of unfiltered x-rays at 40 mm. to an area about 20 mm. in

diameter. This produces a blister in two and one-half or three weeks and takes about five weeks to become quiescent. There is no scar unless a biopsy is done.

DR. G. W. BINKLEY: I should like to ask Dr. Rauschkolb two questions. First, were these lesions present before puberty, and did they accelerate? How old is he? I asked him about his mother, and he stated that she also had several of these.

DR. JOHN E. RAUSCHKOLB: I do not know whether there is a congenital follow-up on this. He is 60 years of age. When he started to have these lesions, he had just about as many of them as he has now. These lesions can be cleared up, and recurrence does not take place in the treated area but in the periphery. In other words, the lesions get larger by being concentric circles. I do not know whether I shall be able to continue to give him contact therapy.

Case for Diagnosis. Presented by DR. H. H. BREMERS, DR. C. GEORGE, and DR. C. SUNIT, for the Department of Urology, University Hospitals, Cleveland.

M. L., a white girl aged 4 years, born and living in Brazil until the end of last year, exhibited what looked like a boil on the right cheek 10 months ago. This burst and discharged pus and did not fully heal. In a few weeks it spread somewhat and showed brownish spots around it. It has been treated by the parents with different ointments, without improvement.

The child is the fourth of five children, all well. Her birth weight was more than 9 lb. (4,082 gm.). From the age of 2½ years she had four or five episodes of chills, fever, anorexia, and pyuria, which lasted 10 or 12 days and cleared without medical treatment. In December, 1951, while the family was on leave at Oberlin, Ohio, she had a similar attack and was admitted to Oberlin Hospital. Roentgenographic examination showed a double pelvis of the left kidney. She was, therefore, admitted to University Hospitals, where on Feb. 18, 1952, a partial nephrectomy was done. She made a satisfactory recovery from the operation, after a short pyrexial course, and is now convalescent.

Systemic examinations otherwise gave essentially normal results. Examination of the skin reveals a lesion on the right cheek, roughly quadrangular, measuring about 2.5 by 2.5 cm., with an irregular central scar, 1 by 1 cm., surrounded by a slightly raised area, covered by fine scales and studded with six to eight pinhead-sized, indurated, flat-topped nodules. Separated from this plaque by a margin of comparatively normal-looking skin and surrounding its medial half are 8 or 10 raised, hemiglobular, brownish, pinhead-sized indolent papules. There is moderate induration. Diascopy does not show characteristic apple-jelly nodules, but seems suggestive of this type of process.

Microscopic examination of a biopsy specimen showed the following: "There is infiltration of the cutis by lymphocytes and occasional plasma cells, a single round focus which shows epithelioid cells, lymphocytes, and a rare, poorly formed giant cell. This focus is sharply circumscribed. Stains for acid-fast bacteria showed no organisms. However, staining was not done at the level of the previously described round focus. This is consistent with lupus vulgaris, but is not diagnostic of it." A kidney biopsy specimen was diagnostic of chronic pyelonephritis with hydronephrosis, chronic ureteritis with recent submucosal hemorrhage, and hydroureter.

Various samples of urine were normal to cloudy, with traces of albumin and a few white blood corpuscles. A serologic test was negative for syphilis. A hemogram showed 4,500,000 red blood cells, a hemoglobin concentration of 14 gm. per 100 cc., and 10,650 white blood cells, with 54 to 50% segmented neutrophiles, 40 to 46% lymphocytes, 0 to 4% monocytes, and 2 to 0% eosinophiles. A test with old tuberculin, 1:1,000, was negative. Scraping of skin did not yield fungous elements on direct examination under the microscope or on culture for three weeks.

No treatment for the skin lesion has yet been undertaken. The patient has had streptomycin and penicillin intramuscularly and chloramphenicol (chloromycetin®) orally during preoperative and postoperative periods.

DISCUSSION

DR. H. HECHT: I think this is lupus vulgaris. The child was born in South America. Milk is the source of many cases. There is no family history of tuberculosis, so far as I could ascertain.

DR. H. H. JOHNSON: Are cases of lupus with a negative tuberculin reaction common?

DR. H. HECHT: It can be that way.

DR. JOHN E. RAUSCHKOLB: From the differential standpoint we have to consider other entities. She was born in Brazil, true, but just outside a large metropolitan city. There is a considerable amount of leishmaniasis there. I would make a smear with Giemsa or Wright stain considering the possibility of leishmaniasis.

DR. G. W. BINKLEY: I also thought of the possibility of a smear showing leishmaniasis and recalled a patient Dr. Cole had 10 or 12 years ago in whom the organisms were beautifully demonstrated in the histologic section. I think that it could be worth while to do this.

DR. H. H. BREMERS: Dr. George has seen more cases of cutaneous leishmaniasis than any of us here.

DR. C. GEORGE: I have seen quite a few cases, and I did not think that the lesions of this patient look anything like the lesions of leishmaniasis I have seen. We made an attempt, with that in mind, to see if we could find Leishmania parasites in the smear but have not succeeded.

Lupus Erythematosus (Chronic Discoid or Chronic Disseminated). Presented by DR. E. H. JONES, Warren, and DR. E. H. JONES JR.

The patient is a 28-year-old white woman, who was first seen in January, 1951, complaining of a mildly pruritic eruption of the forehead, cheeks, and upper chest of one year's duration. The eruption consisted of ill-defined, erythematous papules, mildly edematous areas of the central face and forehead, and small, pale nodules of the upper chest.

The onset was in January, 1950, at which time the patient was pregnant with her second child. The eruption remained essentially stationary until October, 1950, when it became more noticeable but did not involve any new areas. At this time the patient was working in a lamp factory and was exposed to heat and some glare from molten glass.

The blood Kahn and Kline reactions were negative for syphilis. The urinalysis showed a specific gravity of 1.012, an acid reaction, negative reactions for sugar and albumin, no red blood cells, no casts, and many epithelial cells. A hemogram on March 17, 1951, revealed 3,980,000 red blood cells, with a hemoglobin concentration of 11.4 gm. per 100 cc., or 80.3%, and a white blood cell count of 7,550. Another hemogram on Aug. 1, 1951, revealed a hemoglobin concentration of 13 gm. per 100 cc. and 5,700 white blood cells. The sedimentation rate on March 17, 1951, was 19 mm. per hour, and on Aug. 1, 1951, it was 24 mm. per hour. The differential count on Aug. 1, 1951, showed 72% neutrophiles, 19% lymphocytes, 2% eosinophiles, and 6% monocytes. The plasma L. E. test done by Dr. Haserick in August, 1951, was negative. A chest roentgenogram on Aug. 1, 1951, showed nothing abnormal.

Microscopic examination of a biopsy specimen from the forehead on Feb. 13, 1951, was reported as showing "chronic dermatitis consistent with, but not diagnostic of, lupus erythematosus" (Dr. H. Z. Lund).

The patient has received two exposures, each of 50 r, of superficial x-rays, given one week apart, which resulted in no change except alleviation of the mild pruritus. Three per cent iodochlorhydroxyquin (vioform®) cream was applied nightly for several weeks on two different occasions. Gold sodium thiosulfate, 400 mg. in 10 injections at weekly intervals, was given. She has received bismuth sodium triglycollamate ("bistrimate") tablets, two daily, increasing to four daily, since June 1, 1951. For one month, in November, 1951, she received mixed tocopherols, 100 mg. daily. "A-fil" sun-protective cream (a 5% preparation of menthyl anthranilate and titanium dioxide in vanishing cream base) has also been used.

No treatment has influenced the eruption. The sun-protective cream produced a mild accentuation of the erythema on the forehead, and its use was discontinued.

The patient states that she feels chronically tired, although she is able to do all her own housework and care for two small children. On several occasions, both prior to and after the chest roentgenogram, she has noted vague fleeting pains in the chest, apparently unrelated to respirations. Neither the liver nor the spleen has been palpable on repeated examinations.

DISCUSSION

DR. H. N. COLE JR.: On seeing this case for the first time I certainly cannot dispute the diagnosis of lupus erythematosus because I think this is one of the cases that presents a problem in differential diagnosis. When first seen, the condition might fall into the category of lupus

erythematosus, seborrheic dermatitis, or rosacea, but with the treatment the patient has had and the appearance today, I am a little skeptical. I suggest that it might be a seborrheic dermatitis. The patient does have pityriasis of the scalp, and one might give her a therapeutic trial on that basis.

DR. H. N. COLE: She also has steatoma multiplex of Pringle over the sternum, which is not a common disease.

DR. G. M. STROUD: There were a few tiny pustules in several places on the face, and I recommend that these be examined for Demodex organisms.

DR. E. H. JONES JR.: I agree with everything that has been said. When I first saw this patient I thought that the condition was a seborrheic dermatitis and so treated it for two or three weeks, with no response whatsoever.

DR. JOHN R. HASERICK: Dr. J. B. Howell has just written an article regarding lesions associated with lupus erythematosus. He mentioned that lupus erythematosus is frequently misdiagnosed. We apparently do confuse other conditions with lupus erythematosus. As Dr. Jones has pointed out, this confusion is a real problem in management of patients, because if the patient learns that the diagnosis of lupus erythematosus has been made he reads up on it, if he is intelligent, and becomes very frightened. Today I advised the husband to have the patient see Dr. Jones periodically, for reassurance more than anything else. They had become quite frightened and had done their own reading on the subject. The patient was, therefore, in a state of anxiety tension. Since I had had the opportunity of seeing this patient in August, I felt that I could talk with her rather freely. The point we often overlook, even in chronic discoid lupus erythematosus, is that if the diagnosis is made the patient may develop a severe anxiety tension which dominates his life much more than the disease itself.

Congenital Ichthyosiform Erythroderma. Presented by DR. GILBERT BARNES, DR. WOODROW MURPHY, and DR. BERT L. PEPPERCORN, for DR. JOHN E. RAUSCHKOLB.

Adenocystic Basal-Cell Carcinoma of Right Orbit; Tuberculous Pericarditis; Tuberculous Ulcer, Left Leg. Presented by DR. GILBERT BARNES, DR. WOODROW MURPHY, and DR. BERT L. PEPPERCORN, for DR. JOHN E. RAUSCHKOLB.

Keratosis Follicularis (Darier's Disease). Presented by DR. JOHN E. RAUSCHKOLB.

Chronic Discoid Lupus Erythematosus (Profundus Type). Presented by DR. GILBERT BARNES, DR. WOODROW MURPHY, and DR. BERT L. PEPPERCORN, for DR. JOHN E. RAUSCHKOLB.

Urticaria Pigmentosa. Presented by DR. G. W. BINKLEY and DR. H. H. JOHNSON JR.

Pseudoxanthoma Elasticum; Hyperthrophic Pulmonary Osteoarthropathy. Presented by DR. JOHN E. RAUSCHKOLB.

Gouty Arthritis with Tophi. Presented by DR. GILBERT BARNES, DR. WOODROW MURPHY, and DR. BERT L. PEPPERCORN, for DR. ROY SCOTT, Department of Medicine, Cleveland City Hospital.

Multiple Idiopathic Hemorrhage Sarcoma (Kaposi). Presented by DR. GILBERT BARNES, DR. WOODROW MURPHY, and DR. BERT L. PEPPERCORN, for the Department of Surgery, Cleveland City Hospital.

Granulosis Rubra Nasi. Presented by DR. JOHN E. RAUSCHKOLB.

Molluscum Contagiosum of Pubic Region; Verruca Acuminata of Penis; Herpes Zoster of Trunk. Presented by DR. GILBERT BARNES, DR. WOODROW MURPHY, and DR. BERT L. PEPPERCORN, for DR. JOHN E. RAUSCHKOLB.

Obituaries

CHARLES DONEY FREEMAN, M.D.
1879-1952

AMERICAN dermatology lost an outstanding representative, and all who knew him lost a loyal friend when Charles D. Freeman died on April 18, 1952.

Dr. Freeman was born in St. Paul on Jan. 25, 1879. He was graduated in medicine from the University of Minnesota in the class of 1904 and served his internship in the St. Paul Lutheran Hospital. The next two years were spent as an associate of Dr. Egil Boeckmann. He studied under the great dermatological masters of Europe for two years, especially those of Vienna, Paris, and London. Much of the time was spent with the eminent teacher Max Joseph of Berlin. Returning to St. Paul, Dr. Freeman practiced his specialty until his terminating illness began.

As an assistant professor of dermatology at the University of Minnesota, he was a diligent teacher at the Ancker Hospital and the St. Paul Dispensary.

Dr. Freeman was an active member of the Ramsey County Medical Society. He was a member of the American Dermatological Association and the Chicago and Minnesota dermatological societies. He was the first president of the Minnesota Dermatological society. He was a constant attendant at the meetings of the Minnesota Academy of Medicine and was its president in 1933. He was a member of the Minnesota State Medical Association, the American Medical Association, and the Clinical Club of St. Paul. Dr. Freeman was attending dermatologist at the Charles T. Miller, St. Joseph's, and St. Luke's hospitals. He originated the treatment of kerion Celsi with solid carbon dioxide.

He served as a captain in World War I.

Although he was a distinguished physician in every sense of the word, it was as an individual that he attained great esteem in the eyes of his friends. Rarely could one find a man who adhered so strictly to a rigid code of conduct. He staunchly defended his principles and friends and as vehemently condemned what he considered sham or unethical practice. He was abrupt, concise, and, at times, caustic in his manner of speech, but was ever ready to be corrected if shown to be misinformed. He loved life and thoroughly enjoyed to sit at the festive board with his friends, who came from all walks of life. A man, if proved, was a man with Charlie, and he never inquired about origin, creed, or color. He greatly enjoyed fishing, hunting, and bridge and had particular companions for each.

On Jan. 1, 1910, Dr. Freeman married Caroline Boeckmann, the daughter of his greatly respected guide and teacher, and their marriage was an ideal example of devotion, understanding, and mutual admiration. He is also survived by a son, two daughters, and two grandchildren: Charles D., Caroline M. (Mrs. W. D. McCall), Helga B., Willard D. McCall Jr., and Charles Freeman McCall, all of St. Paul.

The friendship of Charlie Freeman and the late Dr. John Butler was one of those rare companionships that became a legend. They attended all medical meetings together; they were close social friends, and they complemented each other in so many ways that they could never be thought of but jointly. Even though they had contrasting personalities, their friendship began in medical school and continued unabated throughout their lives. Charlie thought of Dr. Henry Michelson, of Minneapolis, as his special protégé, and their association was very close.

Dr. Freeman considered life an adventure which was to be experienced without regret or protest. He accepted the good with the bad and believed wholeheartedly in the supremacy of the individual. He neither sought nor would accept patronage, and the mere mention of a socialized order of society brought forth his most vigorous reproach.

One of the most gratifying and proud moments in Dr. Freeman's life was seeing his son assume his dermatological practice in St. Paul and, as Charlie put it, "do well."

He was a grand man with many unique and lovable qualities, and he will be long remembered by his many friends, whose deep sympathy is extended to his surviving family.

JOHN F. MADDEN, M.D.

News and Comment

NOTICES

Addition to Directory of Dermatologic Societies.—The following notice should be added to the Directory of Dermatologic Societies, published in the July issue, page 139:

PAN AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY,
SECTION ON DERMATOLOGY AND SYPHILOLOGY

Joseph J. Eller, President, 745 Fifth Ave., New York (*22*).

William B. Guy, Secretary, 500 Penn Ave., Pittsburgh (*22*).

Place: Floating Medical Congress, *S.S. Nieu Amsterdam* visiting Caribbean countries. Time: Jan. 7-19, 1953.

ANNOUNCEMENTS

On Nov. 21 and *22*, 1952, the University of Minnesota will present a Conference on Pemphigus and the Bullous Dermatoses for dematologists. The one-and-one-half day session will be devoted to the consideration of the pathology, physiology, clinical characteristics, and treatment of the bullous dermatoses.

Several distinguished authorities in this field will participate: Dr. Herman Beerman, Chairman and Professor, Department of Dermatology and Syphilology, Graduate School of Medicine, University of Pennsylvania, Philadelphia; Dr. Walter F. Lever, Assistant Professor, Department of Dermatology, Harvard University Medical School, Boston; and Dr. Stephen Rothman, Professor and Head, Section of Dermatology, University of Chicago. The course will be presented under the direction of Dr. H. E. Michelson, Professor, Department of Medicine, and Director, Division of Dermatology. The rest of the faculty will include members of the clinical staff of the University of Minnesota Medical School and the Mayo Foundation. The conference will be held in the Center for Continuation Study on the University of Minnesota campus.

Housing and meal accommodations are available to registrants in the Center building.

Third Sigmund Pollitzer Lecture.—The Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School announces that the third Sigmund Pollitzer lecture will be given by Prof. Louis F. Fieser on Thursday, Jan. 15, 1953, at 4:00 p. m., in the Main Lecture Hall of the College of Medicine, 477 1st Ave., New York. Prof. Fieser is Sheldon Emery Professor of Organic Chemistry of Harvard University. The title of his talk will be "Role of Cholesterol Compounds in Health and Disease."

Meeting of American Academy of Allergy.—The Ninth Annual Meeting of the American Academy of Allergy will be held at the Statler Hotel, Boston, Feb. *26* to *28*, 1953.

Books

The Scalp in Health and Disease. By Howard T. Behrman, M.D. Price, $12.75. Pp. 566, with 312 illustrations. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1952.

Practically all that is known about the scalp and the scalp hair is reviewed briefly or thoroughly in this excellent volume. As the foreword by Dr. M. B. Sulzberger indicates, dermatologists do not agree with all opinions expressed by the author, however, this volume still remains the most modern and complete treatise on the subject.

There are nine chapters, dealing with embryology, anatomy and physiology, the normal scalp, and preparations applied cosmetically to the hair and the reactions they may produce. The alopecias are discussed thoroughly, including common baldness, cicatrizing alopecias, and alopecia areata. A review of the seborrheic diatheses constitutes another chapter, while various infections pertaining to the scalp are explained in still another chapter. The psychogenic factors and their influence on scalp and scalp hair are discussed thoroughly. Scalp involvement from diseases of the skin and systemic diseases is reviewed. The final chapter reviews new growths involving the scalp, both malignant and benign types. Finally, there is an appendix providing numerous prescriptions that may be given patients with scalp difficulty. A complete bibliography concludes each chapter.

There is little to criticize in this book except so far as all dermatologists may have different opinions regarding classification, etiology, treatment, and influence of the psychogenic factors. Nevertheless, the author gives credit to the opinions of others, as well as defining his own. The book is easily read and is excellent typographically; however, certain of the photographs do not depict clearly the conditions they are supposed to illustrate. This book is highly recommended and should be required reading for dermatologists and all those interested in the scalp, both in health and in disease.

o-o-oh what a relief!
. . . My doctor surely knows what it takes to relieve chafed and irritated skin—and to make my bath a pleasure.
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*Andrews, G. C., "Diseases of the Skin", Ed. 3, 1946, W. B. Saunders Co., Philadelphia.
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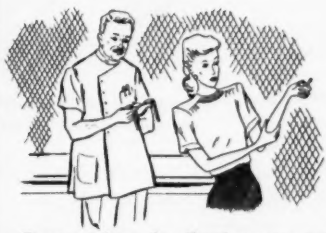

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Abdominal Surgery, Bancroft and Wade, 1947: 804

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Bulletin of the Johns Hopkins Hospital, Sept., 1948: 225-228
The Eye, Ear, Nose and Throat Monthly, April, 1950: 200-203

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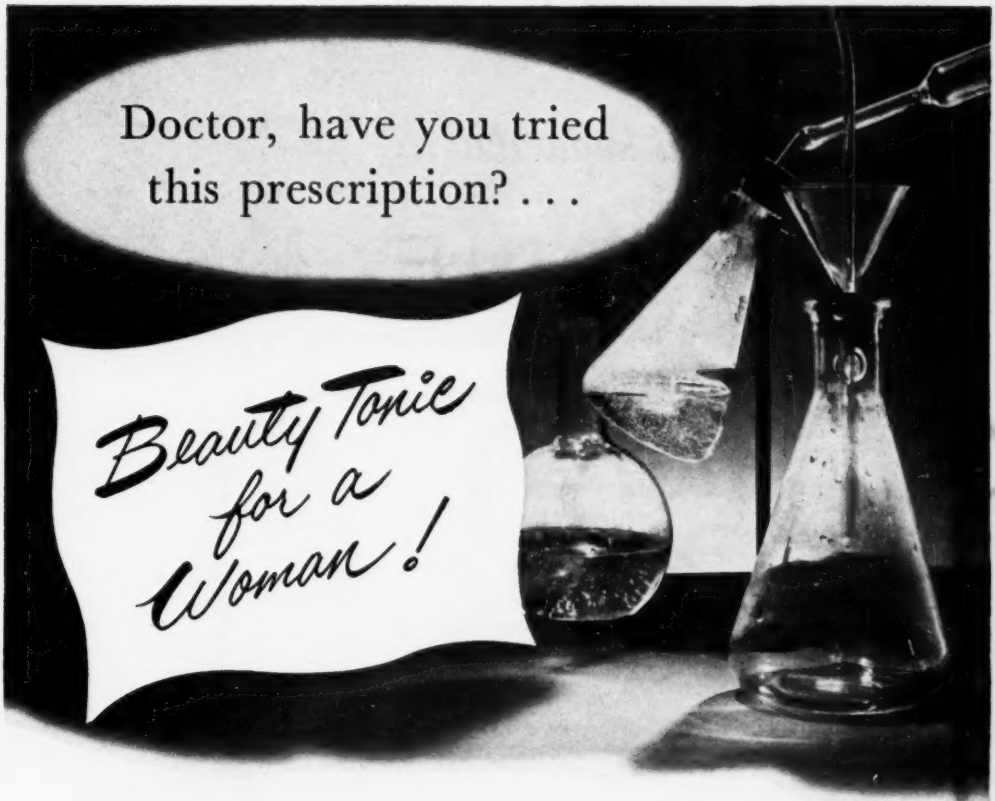

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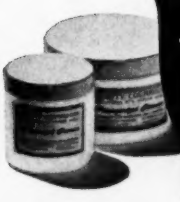

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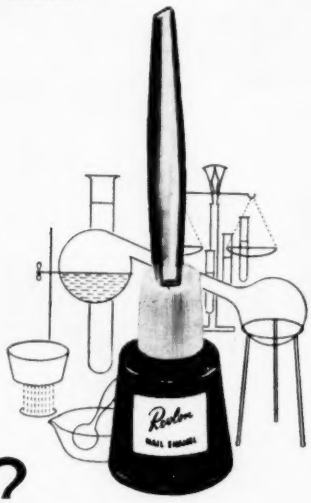

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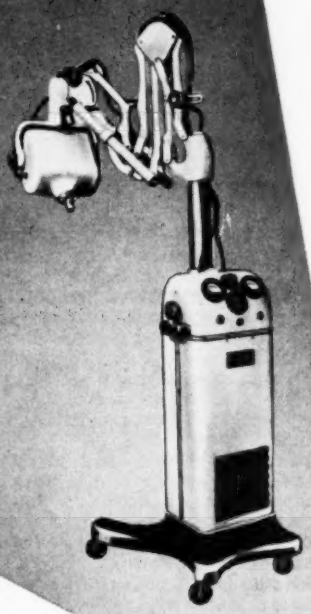

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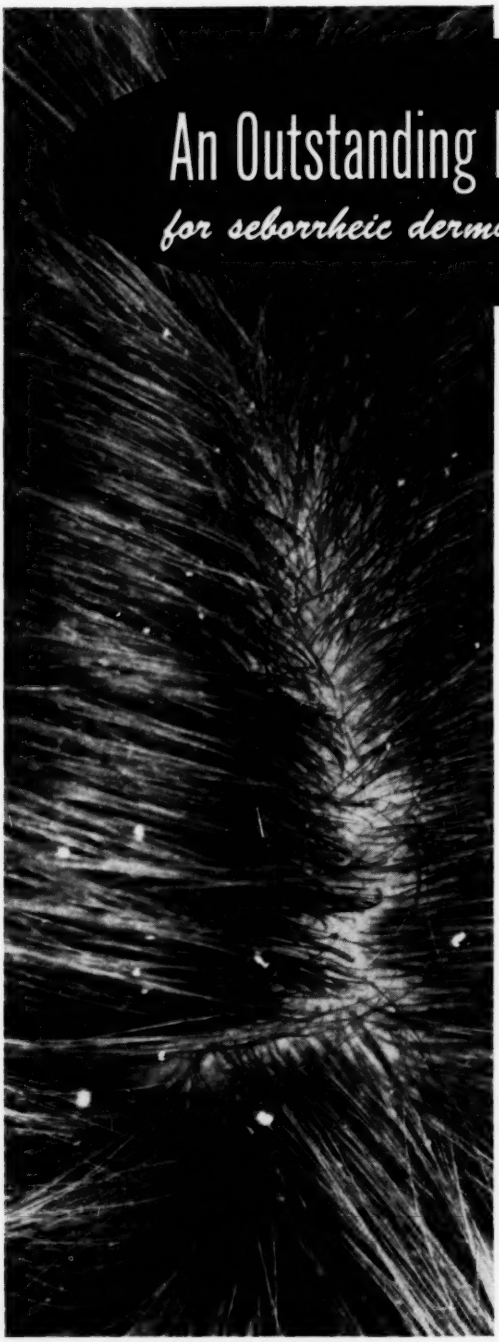

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1. Slinger, W. N., and Hubbard, D. M. (1951), Arch. Dermat. & Syph., 64:41, July.
2. Slepyan, A. H. (1952), *Ibid.*, 65:228, February.
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